MODULE VII: Breast Cancer Treatment

Breast Cancer Prevention

CAN WE PREVENT BREAST CANCER?

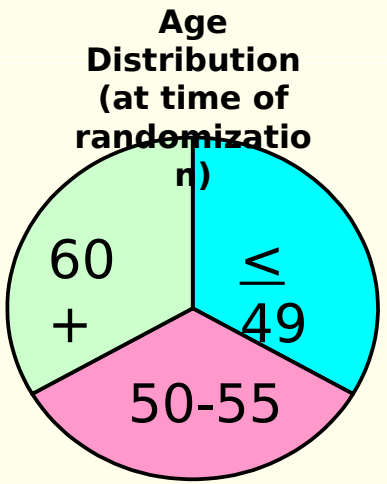
The Tamoxifen Story

TAMOXIFEN CHEMOPREVENTION

- Four clinical trials
  - NSABP P1, P2 (STAR) – ongoing
  - Italian Tamoxifen Prevention Study
  - Royal Marsden Hospital Tamoxifen Prevention Trial
  - International Breast Cancer Intervention Study (IBIS)

NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT (NSABP) BREAST CANCER PREVENTION TRIAL (BCPT)

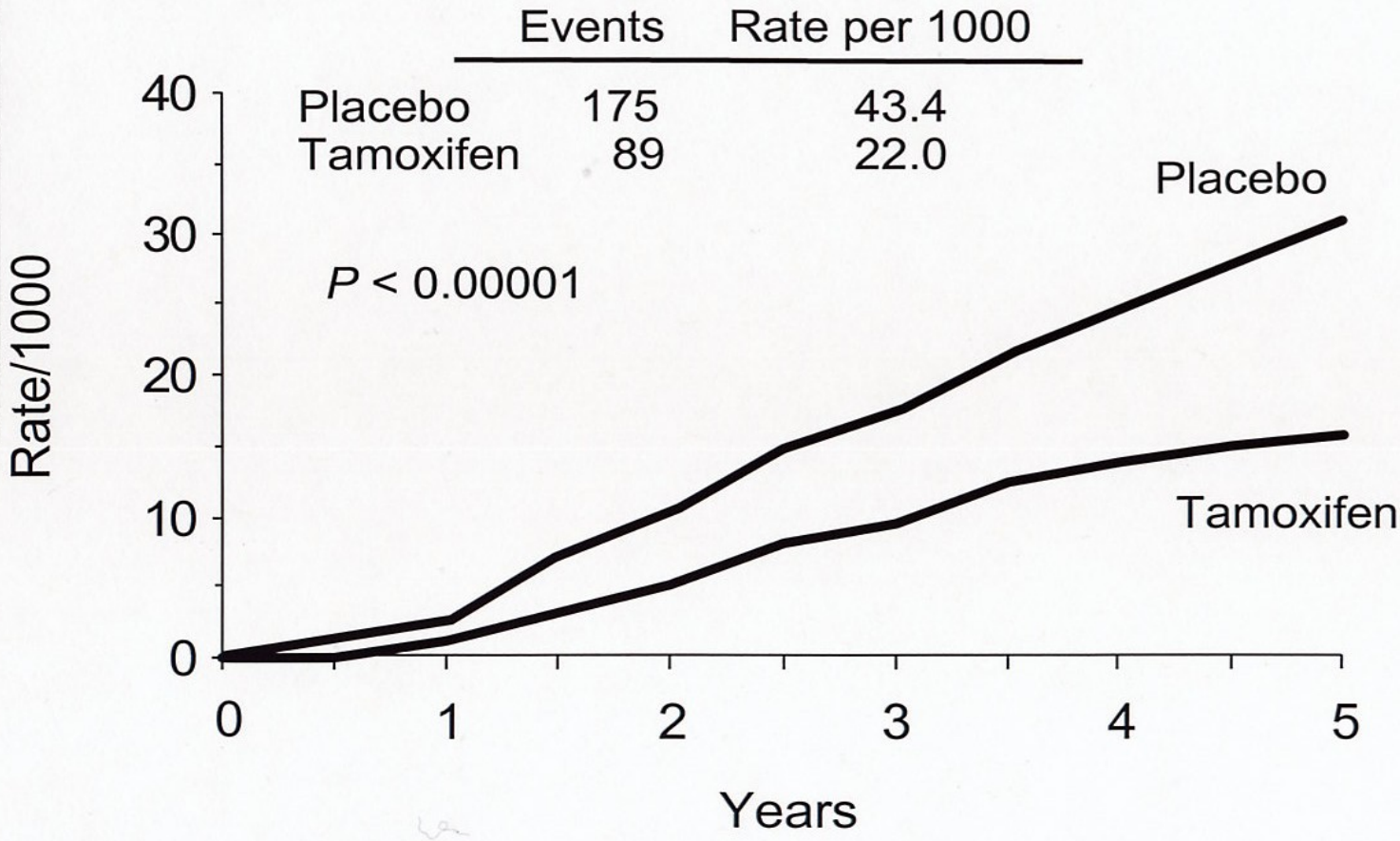
- 13,388 women at increased risk for breast cancer
- Randomized to tamoxifen or placebo (double blind)
- Mean follow-up of about 4 years
- 57% followed four or more years



RISK FACTORS IN BCPT

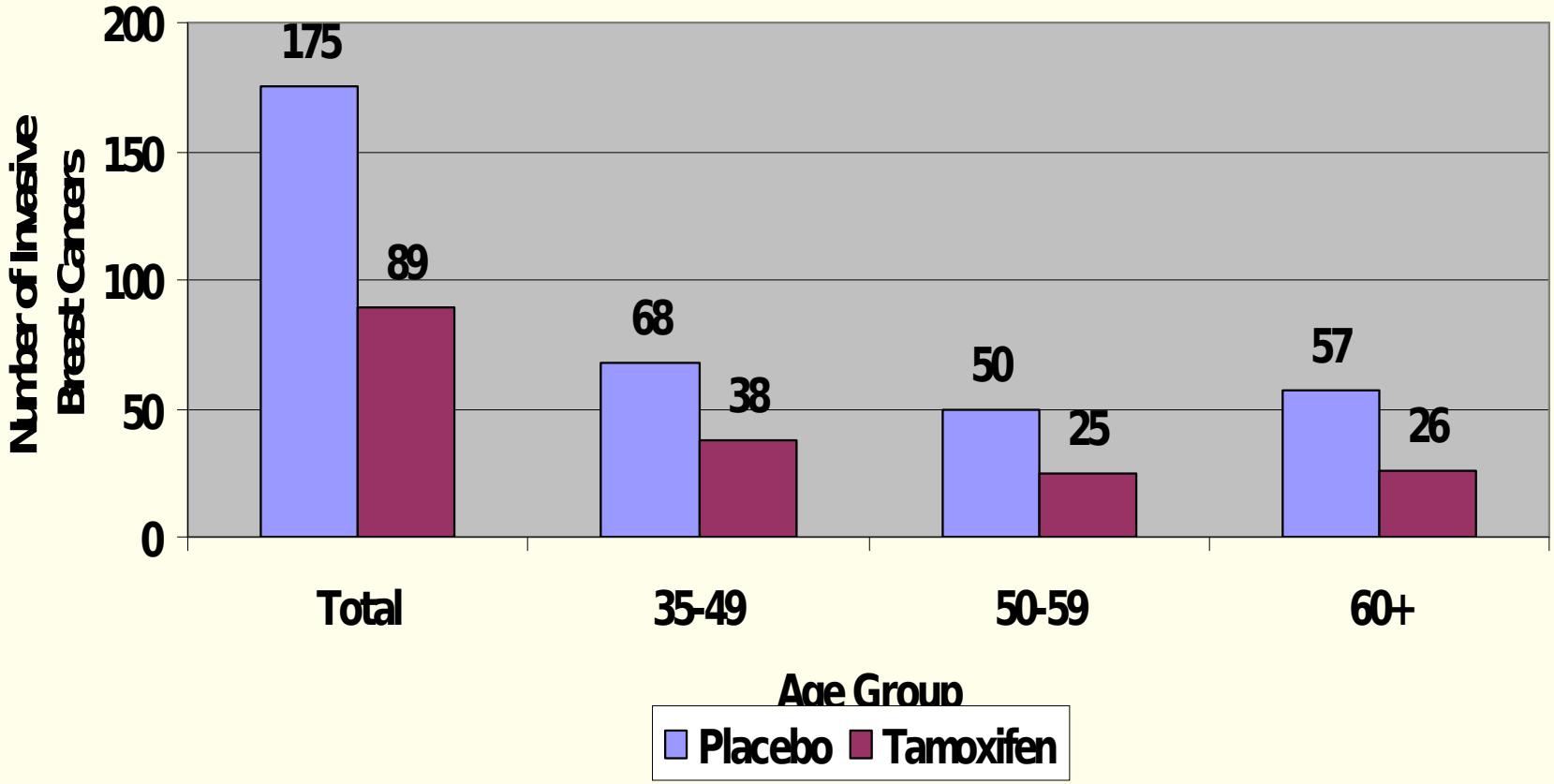
- Age the strongest risk factor
- Other risk factors:
  - Number of affected first degree relatives
  - Number of breast biopsies
  - Atypical hyperplasia / LCIS
  - Age at menarche
  - Age at first live birth
- Women eligible for BCPT if risk is at least equivalent to the average 60 year old woman

BCPT Results: Cumulative Rate of Invasive Breast Cancer



Fisher et al. *J Natl Cancer Inst* 1998;90:1371-1388.

BCPT Results: Invasive Breast Cancer Cases in All Age Groups



Fisher et al. J Natl Cancer Inst 1998;90:1371-1388

BCPT Results: Overview

- Median follow-up 54.6 months (25% of women received 5 years of therapy)
- Tamoxifen group
  - 49% reduction in invasive breast cancer
  - 50% reduction in noninvasive breast cancer*
  - 45% reduction in incidence of hip fractures
  - No effect on ischemic heart disease
  - Increased number of vascular events and endometrial cancer in women over 50

*Analysis included women who had LCIS at baseline.

Fisher et al. *J Natl Cancer Inst* 1998;90:1371-1388.

OTHER TAMOXIFEN PREVENTION STUDIES

Italian Study of 5408 women, ages 35 - 70

- All women had had hysterectomy
- Not designed to target high risk women
- Hormone replacement therapy allowed
- No benefit from Tamoxifen

Royal Marsden Trial, 2494 women, ages 30 - 70

- High risk women: positive family history
- Hormone replacement therapy allowed
- No benefit from Tamoxifen

IBIS

- 7000 women at increased risk of breast cancer age 35-70
- Tamoxifen or Placebo for 5 years
- There were 101 cases of breast cancer in the placebo group and 69 in the Tamoxifen group
- Tamoxifen reduced the risk of breast cancer by 33%, p=0.01

SIDE EFFECTS OF TAMOXIFEN

- Endometrial Cancer (<1%)
- Blood clots (1/1000)
- Hot flashes - in 15-20%
- Vaginal discharge
- Cataracts

SIDE EFFECTS OF TAMOXIFEN: ENDOMETRIAL (UTERINE) CANCER

- The risk is 3 times greater in women taking Tamoxifen than in women taking placebo
- Less than 1 in 1000 women on Tamoxifen developed endometrial cancer
- Uterine cancer is usually detected at a very early stage; most women are cured
- Vaginal bleeding is an early sign of this cancer
- Regular Pap smears offer early detection

INCIDENCE OF BLOOD CLOTS WITH TAMOXIFEN
% OF WOMEN DEVELOPING CLOTS WITH 5 YEARS OF PLACEBO OR TAMOXIFEN

	Placebo	Tamoxifen
DVT	0.084%	0.134%
PE	0.023%	0.069%

Although the relative risk of blood clots increased with Tamoxifen, the absolute risk was still very small.

y about 1 in 1000 women taking Tamoxifen developed a blood c

Women with a High Likelihood Positive Net Benefit Tamoxifen

- In **general**, women who:
  - Have a very high breast cancer risk (have had LCIS, DCIS, or atypical hyperplasia **or** have a 5-year breast cancer risk of ≥ 6.5%), **or**
  - Are less than age 50 and have a 5-year breast cancer risk of ≥ 1.66%, **or**
  - Are over age 49, without a uterus and at low risk for thromboembolic events, and have a 5-year breast cancer risk of ≥ 1.66%

Tamoxifen for Reduction of Breast Cancer Incidence: Contraindications

- Tamoxifen should **not** be taken by women who:
  - Are pregnant or currently planning to become pregnant
  - Require concomitant anticoagulant therapy
  - Have a history of DVT or PE

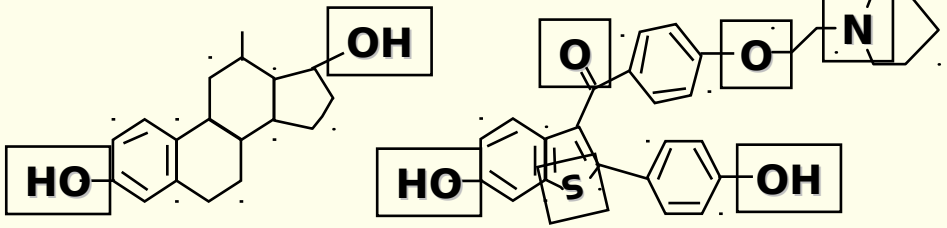
Is there anything better than Tamoxifen for Prevention?

Multiple Outcomes of Raloxifene Evaluation (MORE) Trial

- 7705 postmenopausal women with osteoporosis
- Designed to examine risk of fracture vs placebo
  - Secondary end point: breast cancer incidence
  - Baseline breast cancer risk not assessed
- Two treatment groups (60 mg and 120 mg) - data pooled
- Preliminary results at 40-month follow-up:
  - 76% reduction in incidence of newly diagnosed invasive breast cancer
  - No increase in endometrial cancer, but low number of events

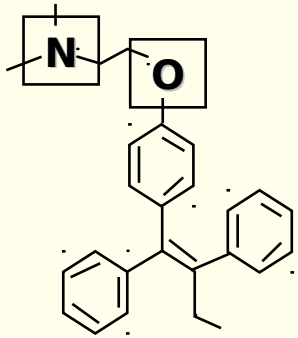
Cummings et al. *JAMA* 1999;281:2189-2197.

Chemical Structure of Estradiol and Selected SERMs

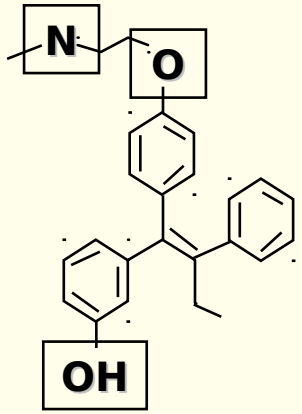


Estradiol

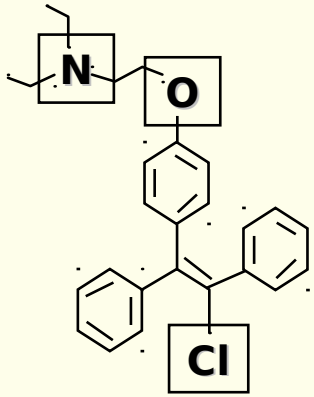
Raloxifene



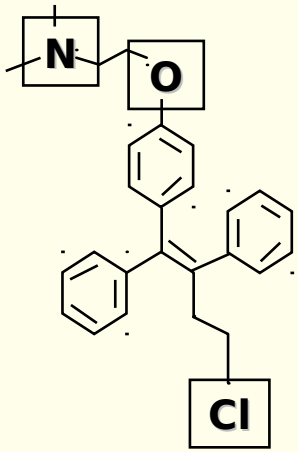
Tamoxifen



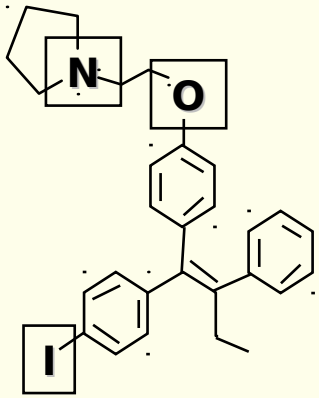
Droloxifene



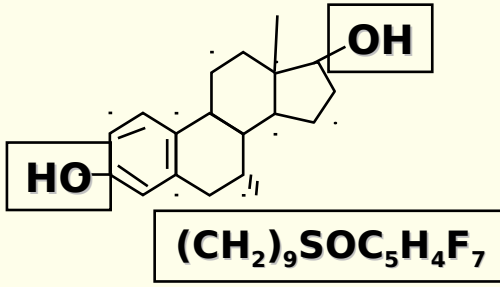
Clomiphene



Toremifene



Idoxifene



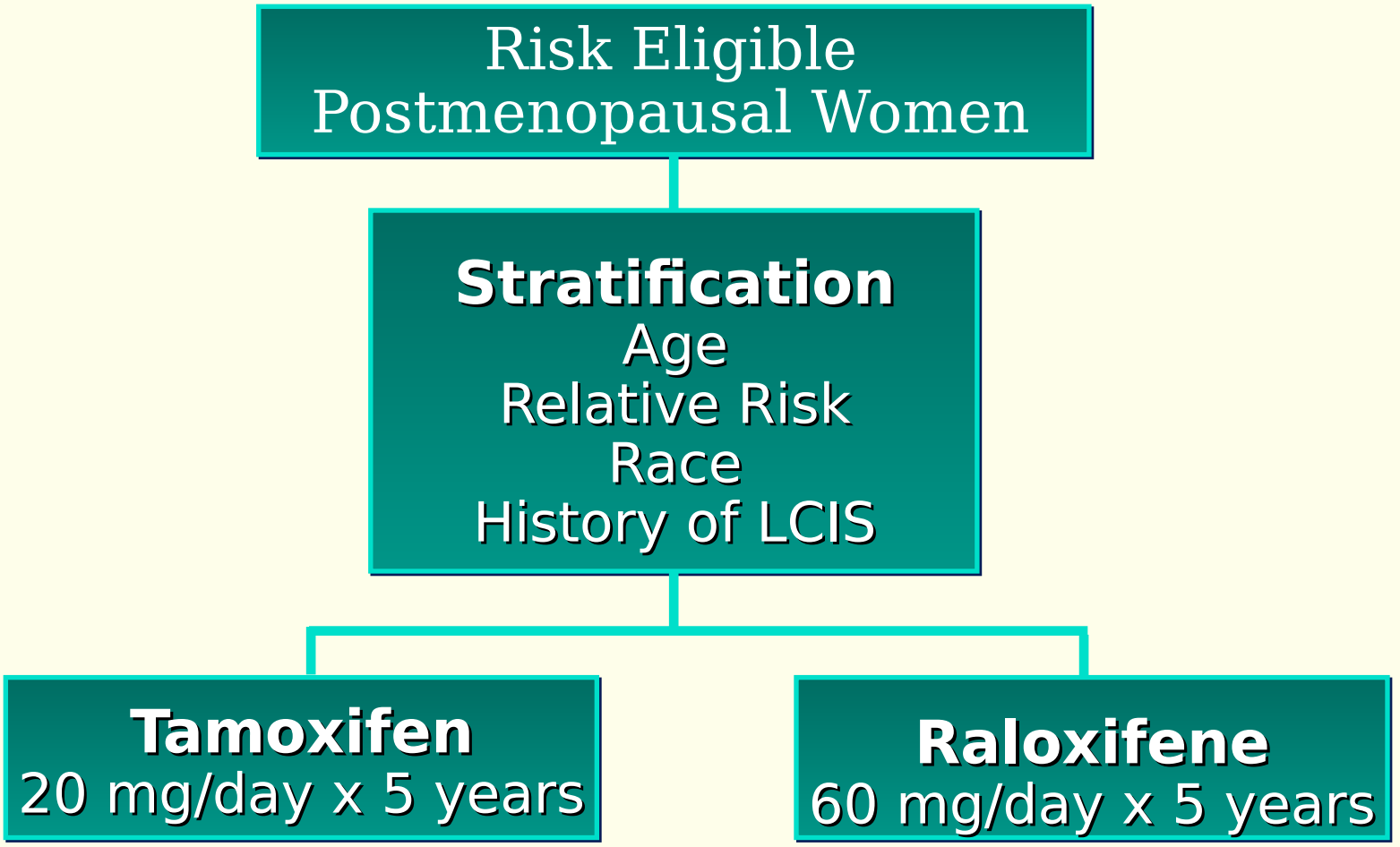
ICI 182,780

Raloxifene & Tamoxifen Trials

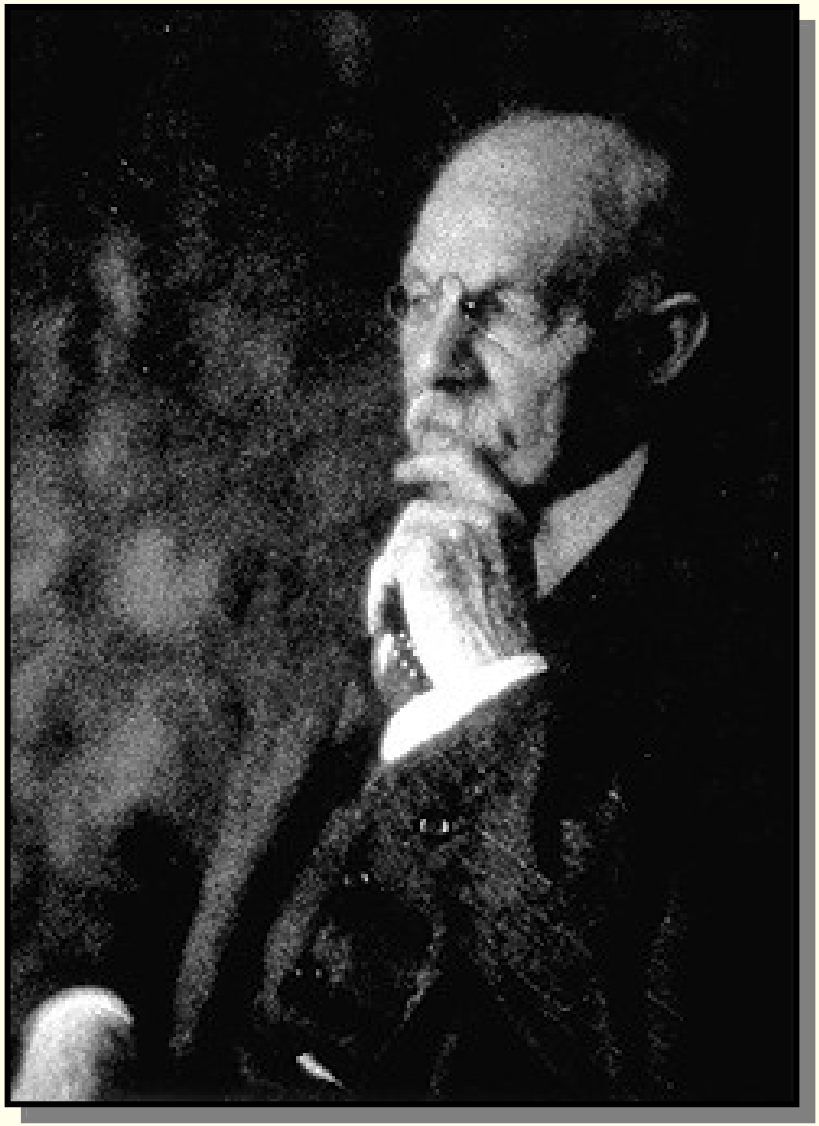
Antiestrogenic and Estrogenic Activities of Raloxifene and Tamoxifen

Tissue	Tamoxifen	Raloxifene
Tamoxifen		
Breast	AE	AE
Vagina	AE	AE
CNS	AE	AE
Bone		E
	E	
Liver	E	E
Endometrium	AE	E

NSABP Protocol P-2 Schema
"STAR" Trial



History of Breast Cancer Treatment



Dr. William Halstead

Halsted's Belief

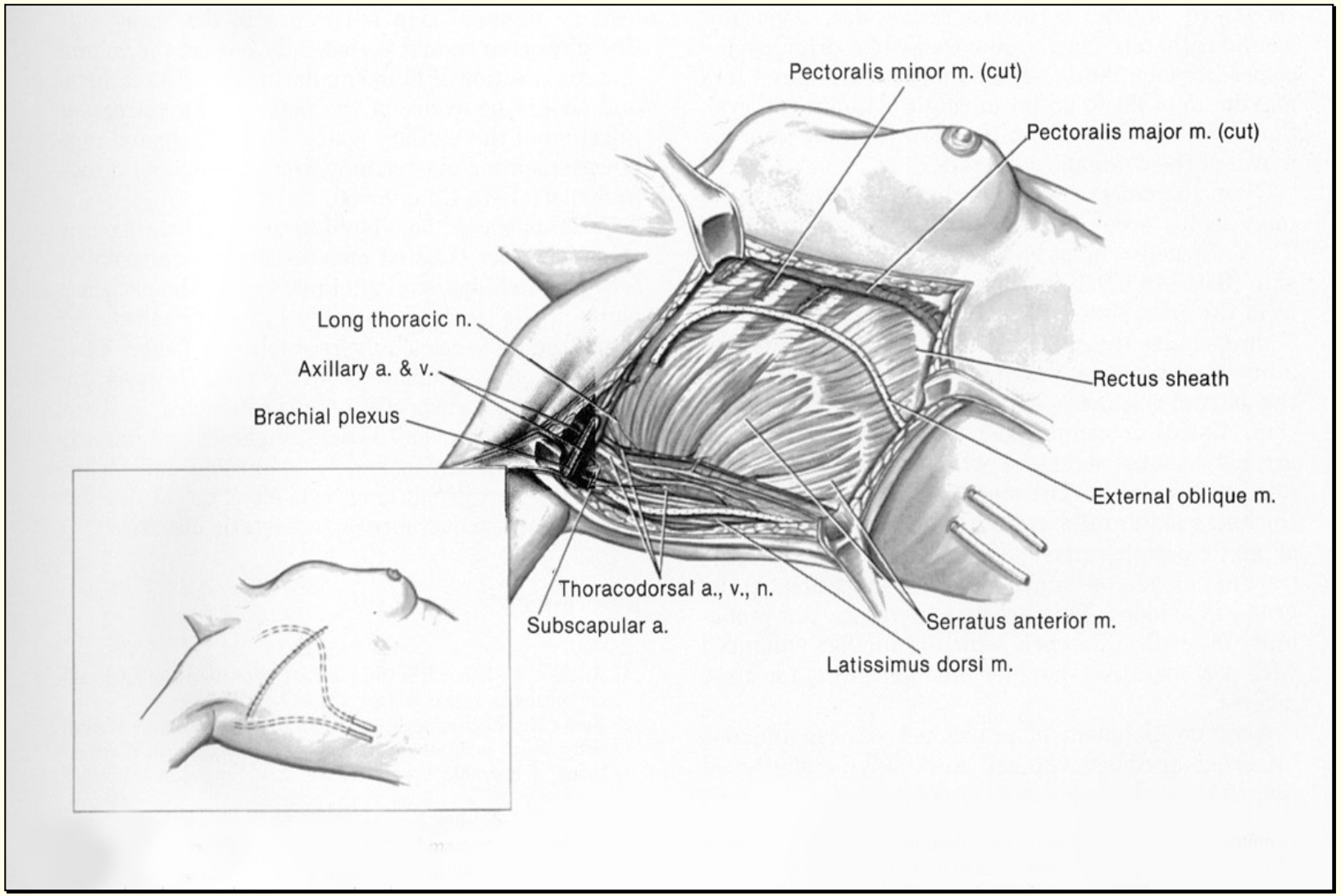
"a cure … is not only possible, but, if operated upon early, quite probable"

Halstedian Principles of Breast Cancer Surgery

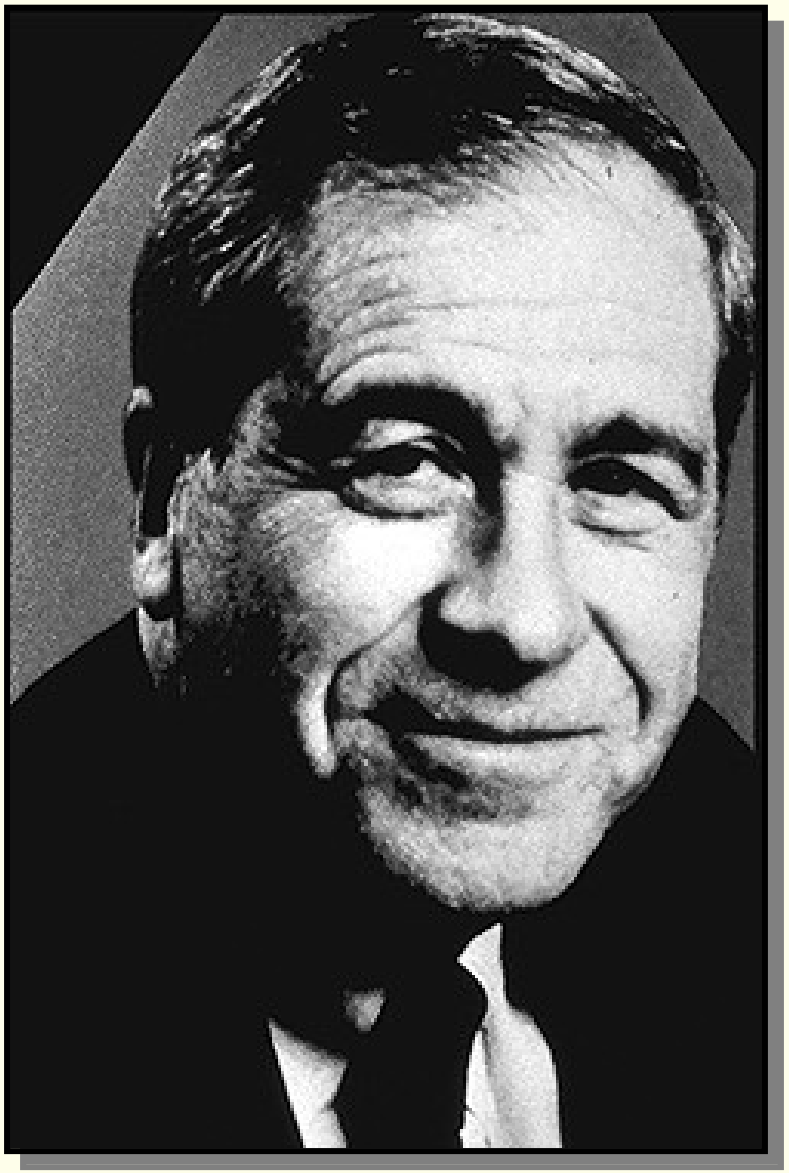
- Anatomic basis for the spread of breast cancer
- Orderly progression of tumor spread:

  Breast → Lymph Nodes → Distant Sites
- Treatment failure = inadequate surgical procedure

Halstedian Mastectomy



Halstead Mastectomy



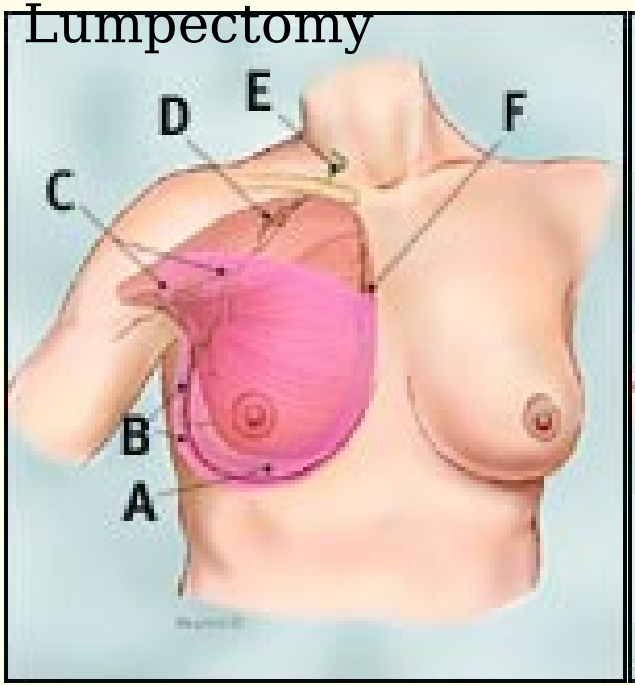
Dr. Bernard Fisher

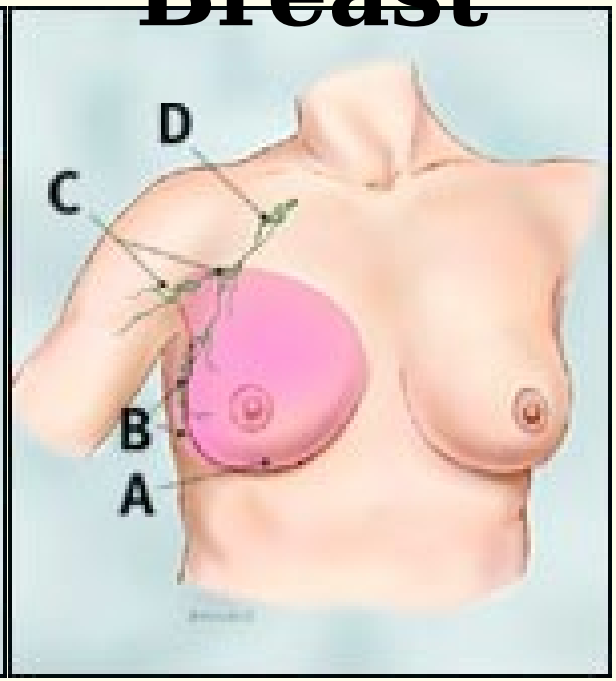
Alternative Fisher Hypothesis

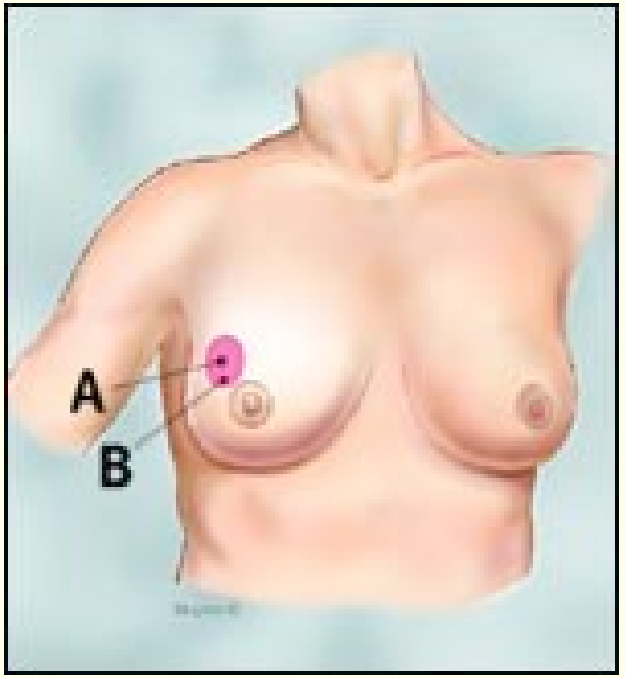
- Systemic at diagnosis
- Complex host-tumor relationships
- Outcome unaffected by local treatment variations

Evolution of the Surgical Management of the Breast

Halstead Mastectomy → Mod Radical Mastectomy → Lumpectomy



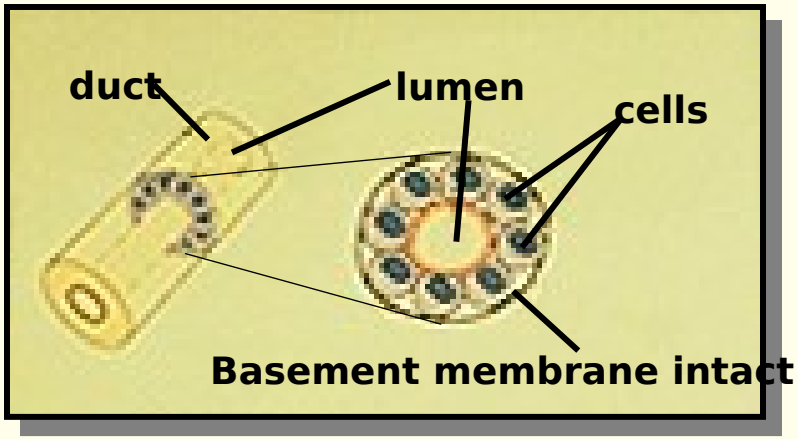




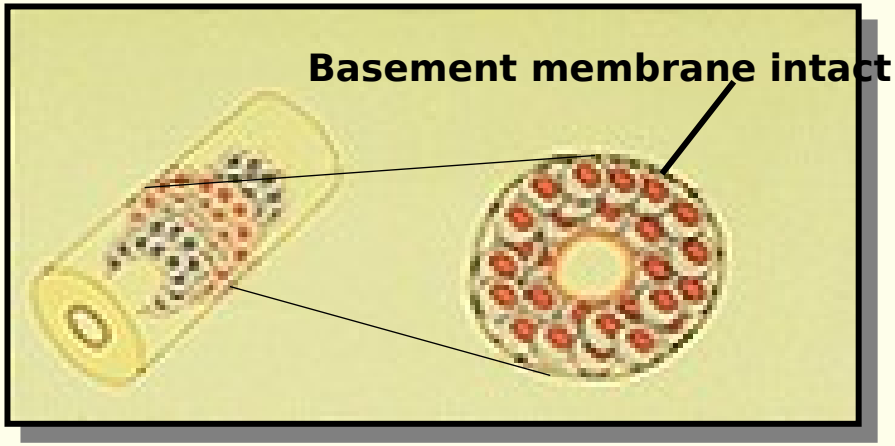
Diagnosis of Breast Cancer

Methods of Tissue Sampling

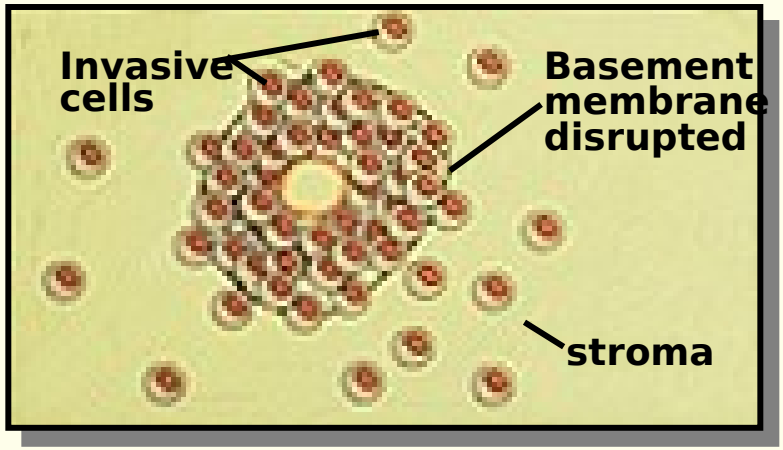
- Fine needle aspiration (FNA)
- Biopsy with needle guidance
- Biopsy of palpable mass
- Incisional biopsy



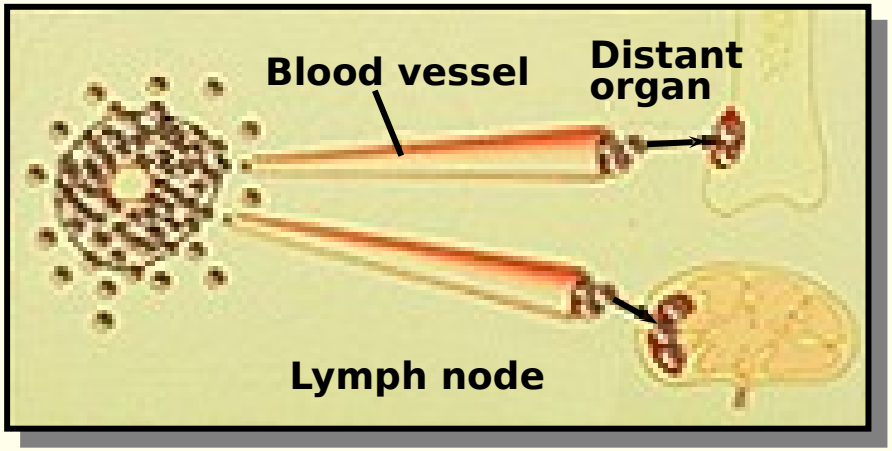
Normal



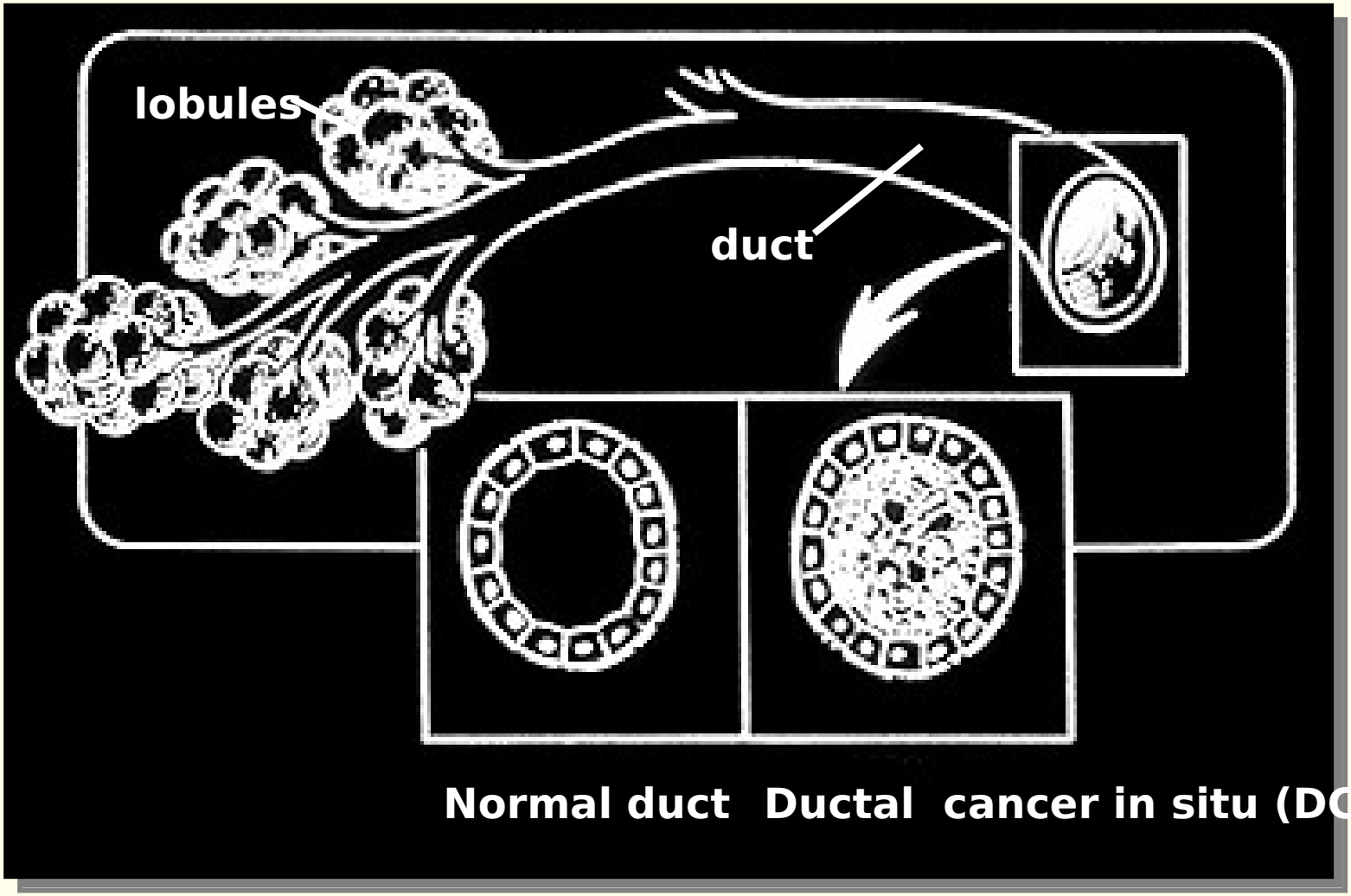
In situ cancer

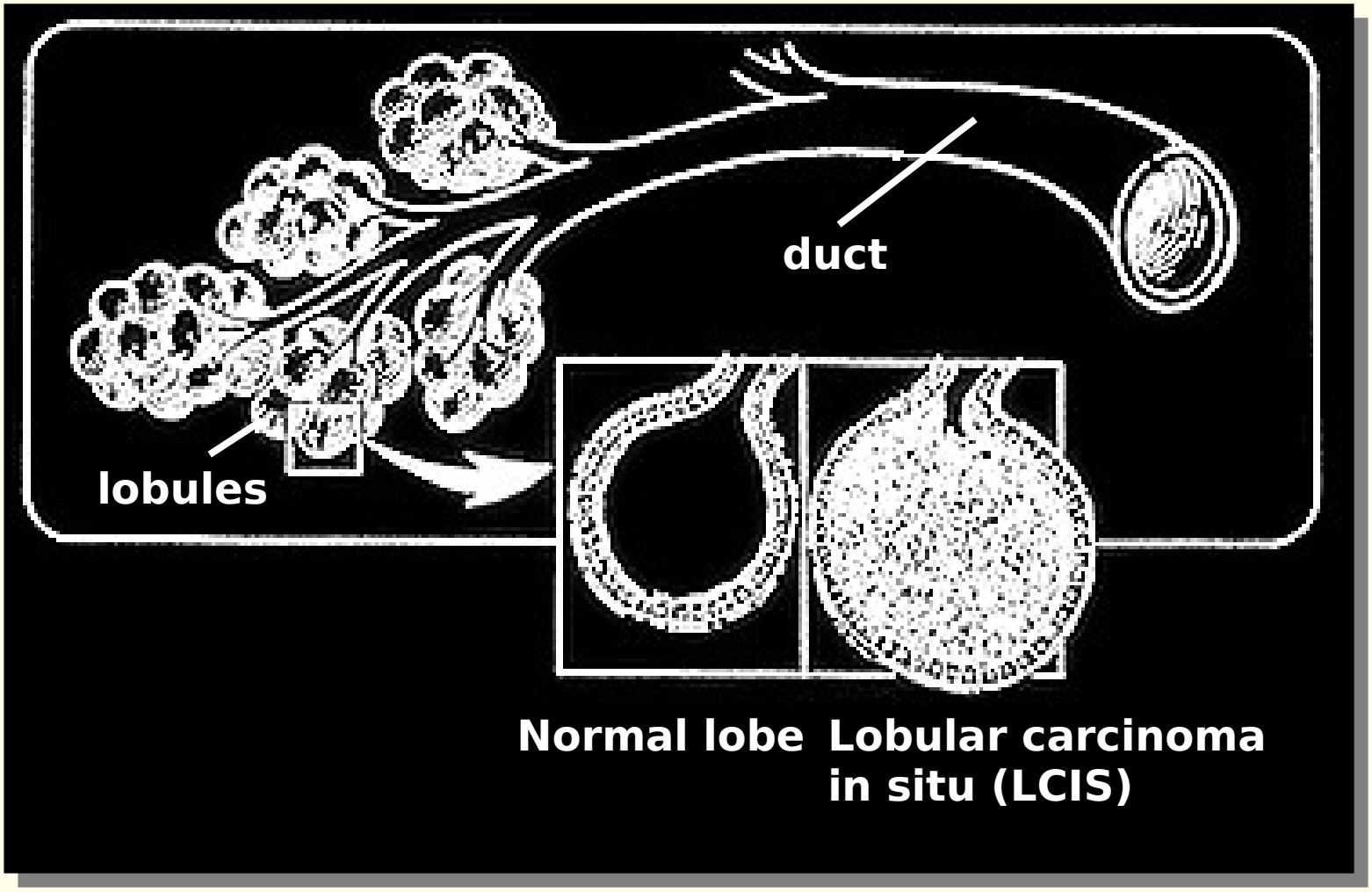


Invasive cancer

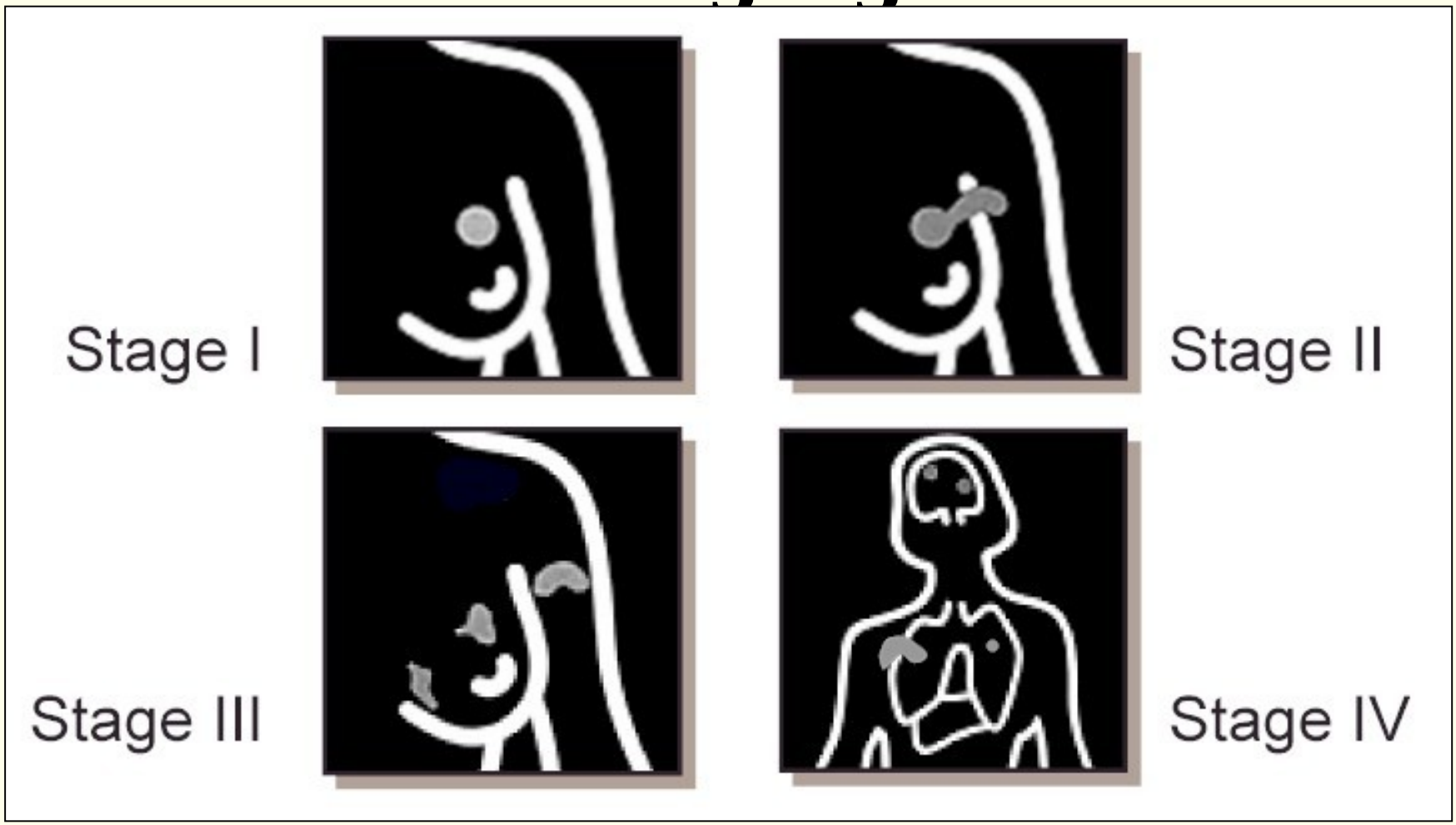


Metastatic cancer


lobules
duct
Normal duct
Ductal cancer in situ (DCIS)


duct
lobules
Normal lobe
Lobular carcinoma
in situ (LCIS)

Breast Cancer Pathologic Staging



AJCCS, 1977

BREAST CANCER STAGING

TNM Classification

T
Primary Tumor

T_x
- primary tumor cannot be assessed

T_o
- no evidence of primary tumor

T_{is}
- carcinoma in situ; intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of nipple with no invasion.

T_1
- tumor < 2 cm in greatest dimension

T_{1a} < 0.5 cm T_{1b} > 0.5 cm, < 1.0 cm
T_{1c} > 1.0 cm, < 2.0 cm

T_2
- tumor 2-5 cm in greatest dimension

T_3
- tumor >5 cm in greatest dimension

T_4
- fusion to chest wall
- edema, peau d' orange
- ulceration of skin
- satellite skin nodules
- inflammatory breast cancer

N
Lymphatic Spread

N_x
- regional lymph nodes cannot be assessed

N_o
- no palpable regional lymph nodes

N_1
- palpable ipsilateral axillary lymph nodes, movable

N_2
- palpable ipsilateral axillary lymph nodes, fixed

N_3
- Ipsilateral internal mammary or supraclavicular nodes

M
Distant Metastases

M_x
- distant metastases cannot be assessed

M_o
- no distant metastases

M_1
- distant metastases present

Stage	T	N	M
0	T_x	N_0	M_0
I	T_1	N_0	M_0
IIA	T_0	N_1	M_0
	T_1	N_1	M_0
	T_2	N_0	M_0
IIB	T_2	N_1	M_0
	T_3	N_0	M_0
IIIA	T_0	N_2	M_0
	T_1	N_2	M_0
	T_2	N_2	M_0
	T_3	N_1, N_2	
IIIB	T_4	N0, N1, N2	M_0
IIIC	Any T	N_3	M_0
IV	Any T	Any N	M_1

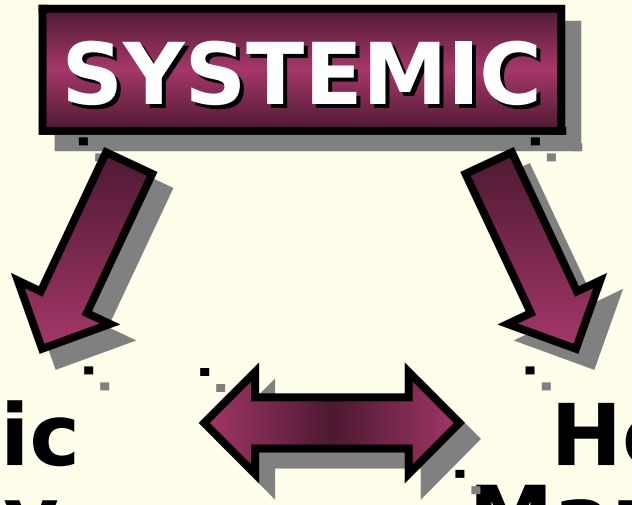
Treatment Options

Current Methods to Effect Survival

- **Detection of disease in premetastatic phase**
- **Local treatment to the breast**
- **Administration of system therapy to eradicate micrometastasis**

Mastectomy

Breast Conserving Therapy



Systemic Therapy

Hormonal Manipulation

Mastectomy

Breast Conserving Therapy

Surgery

Breast Cancer
Local Therapy

- Ductal Carcinoma in-situ (DCIS)
  - Total Mastectomy vs. Breast Conserving Therapy
- Invasive Breast Cancer
  - Modified Radical Mastectomy vs. Breast Conserving Therapy

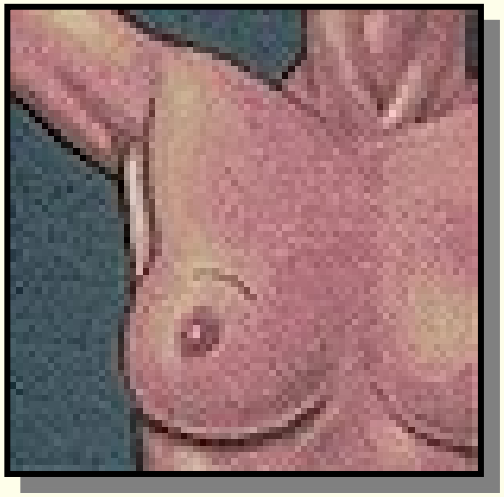
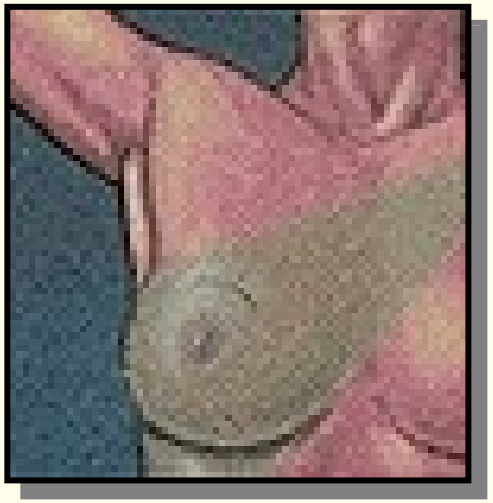
DCIS

- Total Mastectomy
  - No axillary lymph nodes removed
  - >97% Cured
  - Used in diffuse disease

DCIS

- Lumpectomy and Radiation Therapy
  - No randomized trial comparing it to mastectomy
  - High survival rates
  - Addition of radiation decreases recurrence for both invasive and non-invasive cancers

NSABP B-17 / EORTC

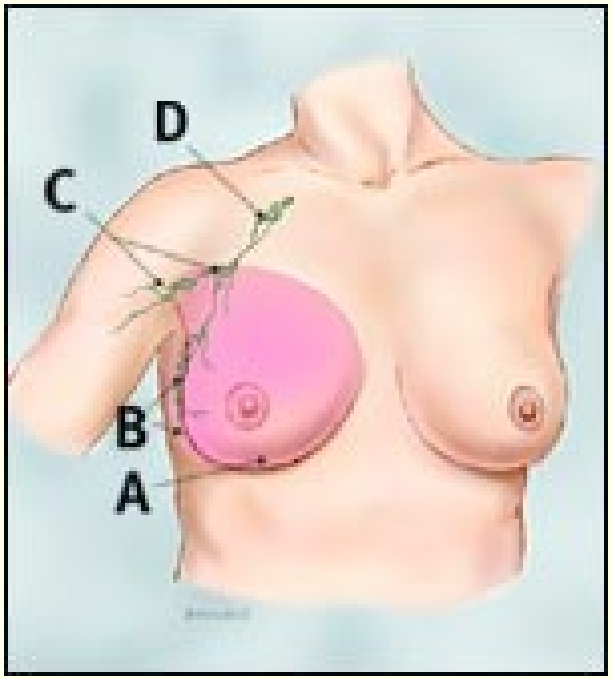
	Lumpectomy		Lumpectomy + RT
		vs.	
Non-invasion Recurrence	13.4% / 8%		8.2% / 5%
Invasive Recurrence	13.4% / 8%		3.9% / 4%

Local Therapy, cont.

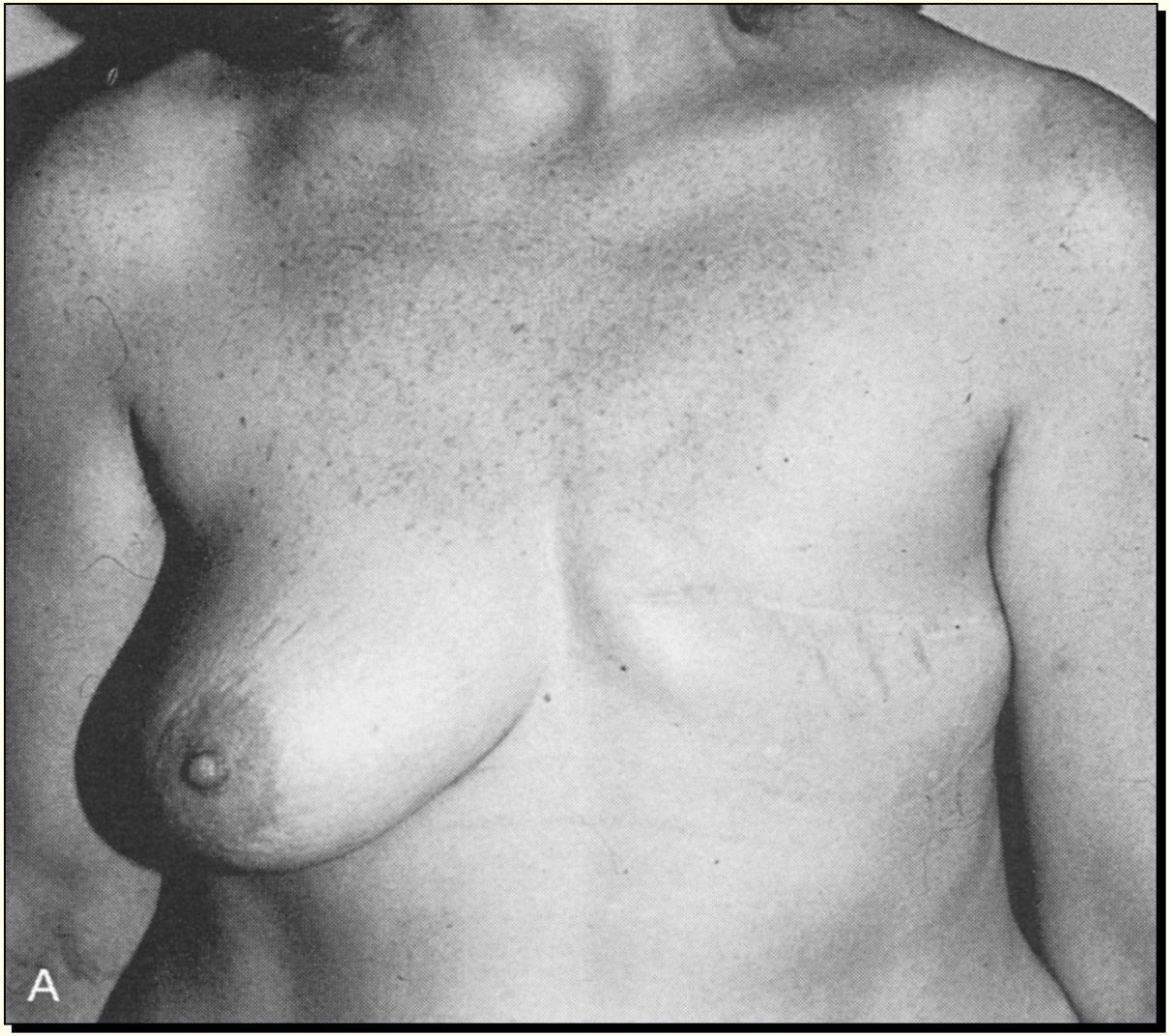
- Invasive Breast Cancer
  - Modified Radical Mastectomy vs. Breast Conserving Therapy

Modified Radical Mastectomy

- Guy's hospital 1977
  - 534 women, radical mastectomy vs. MRM
  - At 11 yrs no difference in survival
- Alabama BCP 1983
  - 311 women, RM vs. MRM
  - At 10 yrs no difference in survival



Modified Radical Mastectomy



Reasons For Mastectomy

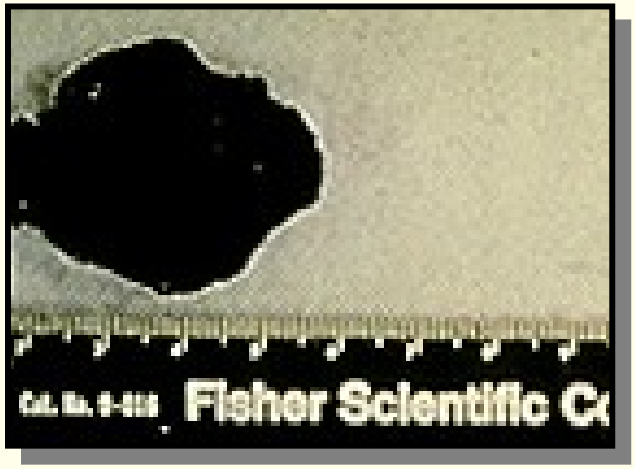
- **Large tumor > than 5 cm**
- **Diffuse suspicious microcalcifications**
- **More than 1 tumor in the same breast (multicentric disease)**
- **Inflammatory Breast Cancer**
- **Persistent positive margins on wide local excision**
- **Patient is pregnant**
- **Previous radiation therapy to the breast which has cancer**
- **Poor cosmetic results predicted (ratio of tumor volume to breast size)**
- **Personal preference**

Breast Conserving Therapy
Historical Aspects

- NCI-Milan 1981
  - 701 women MRM vs. BCT (quadrantectomy and radiation therapy)
  - No difference in survival at 10 yrs
- Multiple subsequent large international prospective randomized trials confirmed that BCT provides equivalent survival to MRM

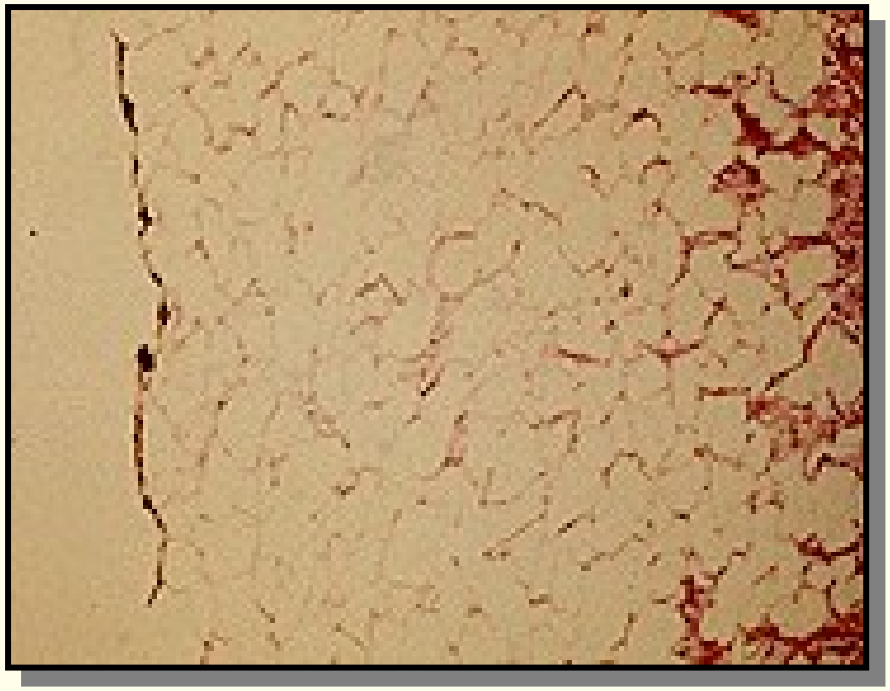
Breast Conserving Therapy "Lumpectomy"

Breast Conserving Therapy "Lumpectomy"



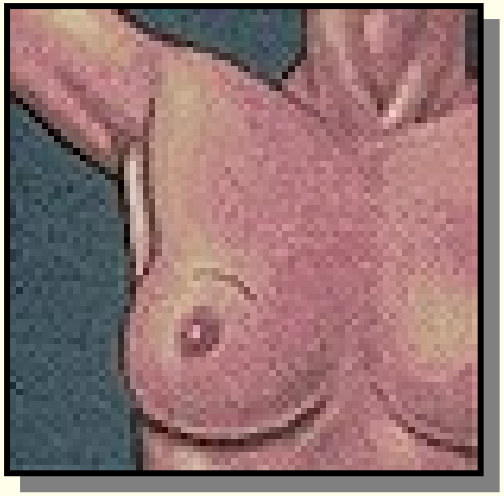
Pathology – Margin Status

(+)
Margin



(-)
Margin

NSABP B-06 10 Year Reanalysis

Lumpectomy + Axillary Dissection		Lumpectomy + Axillary Dissection & RT		Mastectomy
	vs.		vs.	

n	719	731	713
IBTR	40.9%	12.4%	Not applicable
Survival	65%	71%	68%

Invasive Breast Cancer Mastectomy vs. BCT Trials

	Local Recurrence (%)		Overall Survival (%)		
Trial	BCT	M	BCT	M	F/U (Years)
NSABP B-06	12	8	63	59	15
Milan I	7	4	65	65	18
NCI-US	16	6	77	75	10
EORTC	20	12	65	66	10
IGR	9	14	73	65	10
Danish	5	6	79	82	6

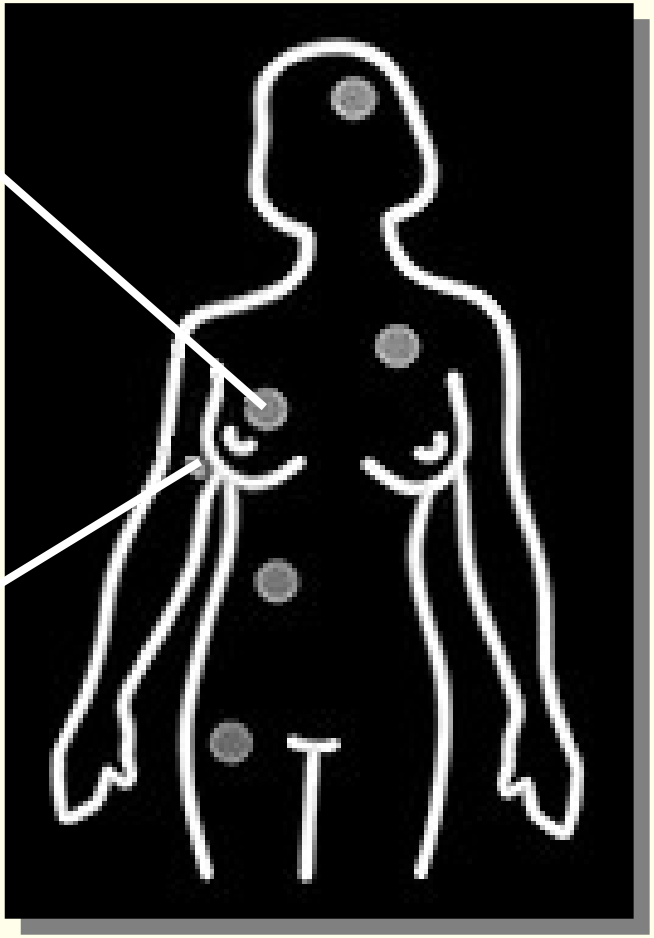
Breast conserving therapy (lumpectomy with radiation) is equal to mastectomy for local treatment.

Axillary Lymph Nodes

Potential Micrometastases At Time Of Initial Diagnosis

Initial site

Lymphatic marker



Possible Micrometastatic Sites

- Lymph nodes
- Lung/Pleura
- Liver
- Brain
- Bone
- Adrenals

Axillary Lymph Nodes Assessment

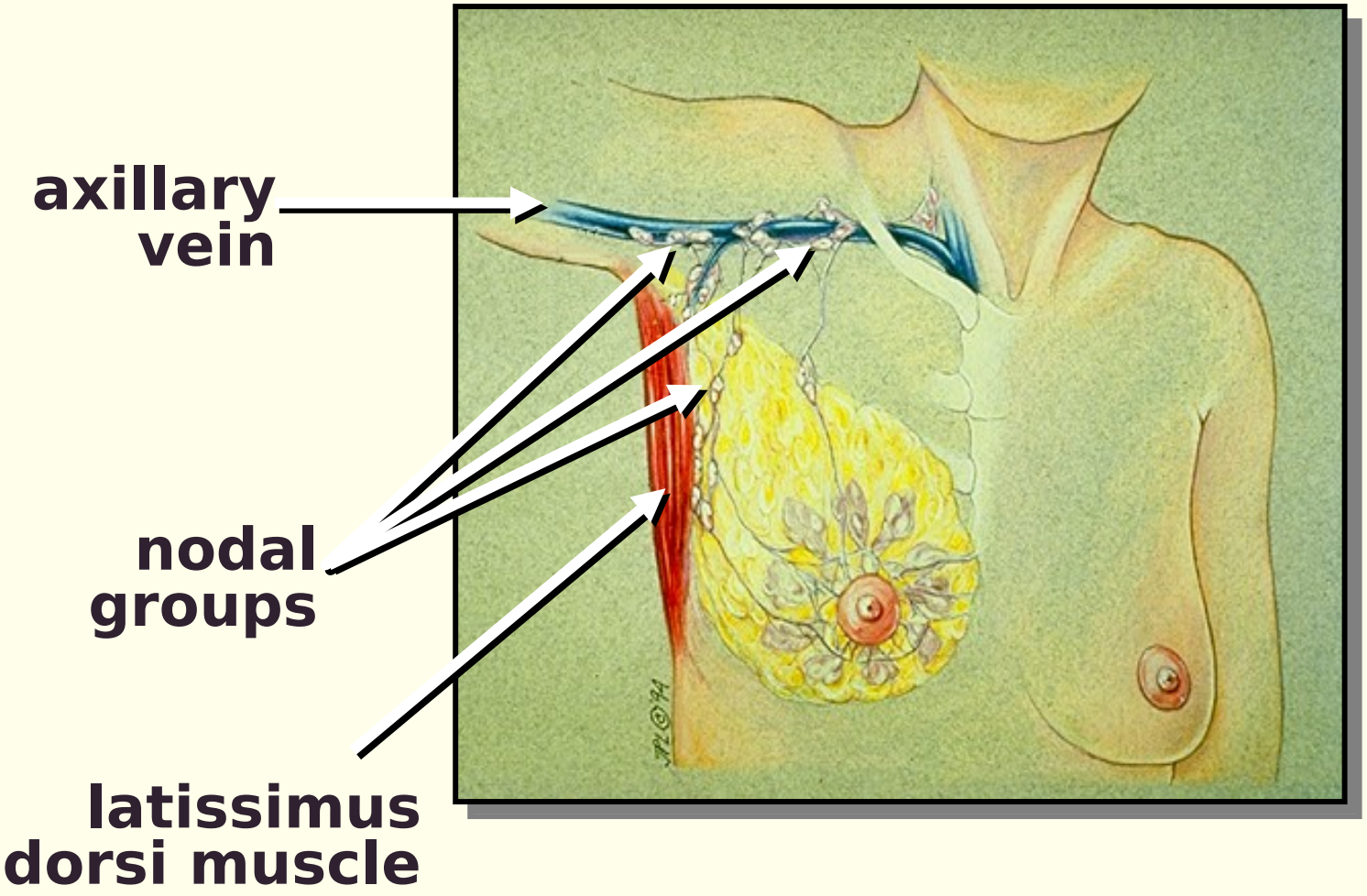
Why bother?

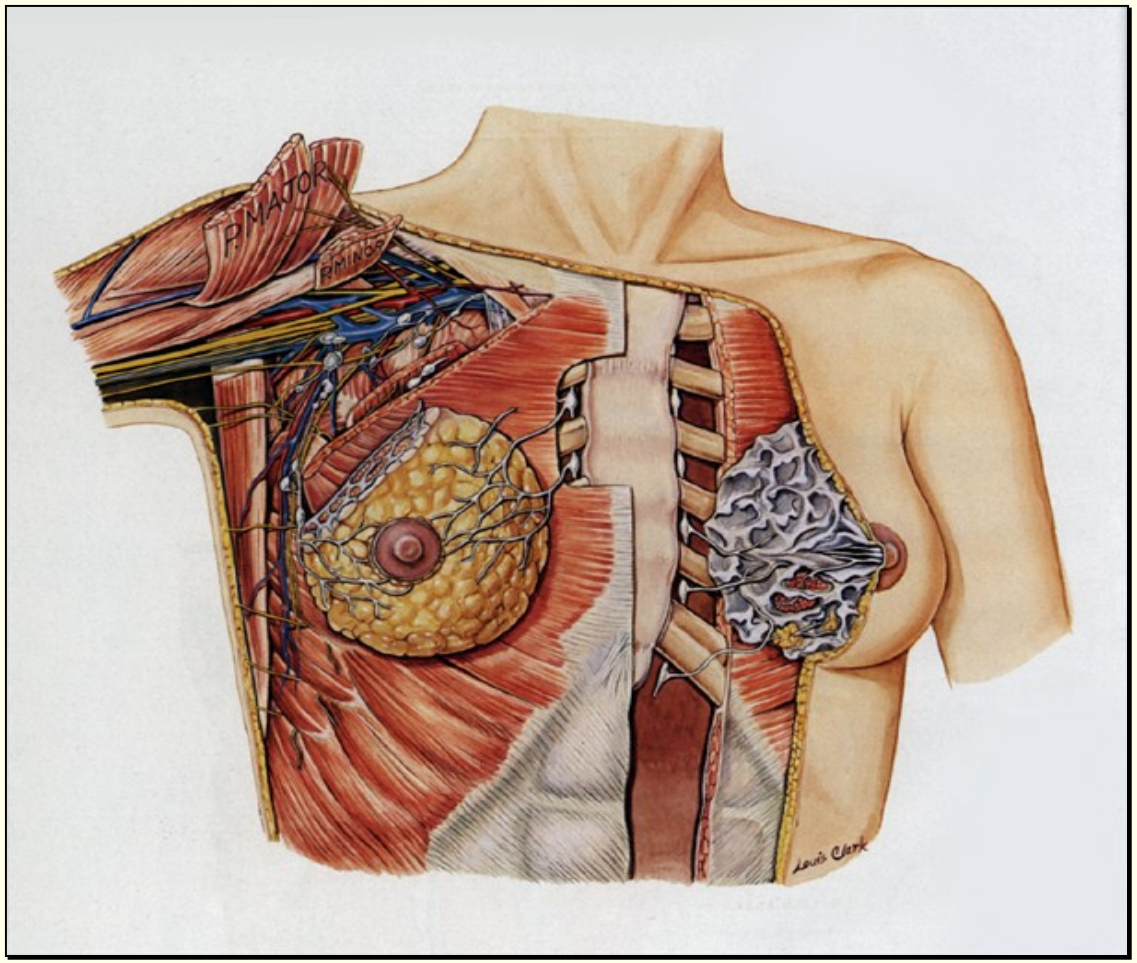
- Strongest prognostic indicator
- Local control
- Guides adjuvant therapy

BUT

- Currently, no appreciable effect on survival

Axillary Lymph Nodes





Level 1: Lateral to pectoralis minor
Level 2: Under pectoralis minor

Complications of Axillary Dissection

- Numbness
- **Lymphedema**
- Poor range of motion
- Infection risk
- Chronic pain
- Nerve injury / weakness

Lymphedema

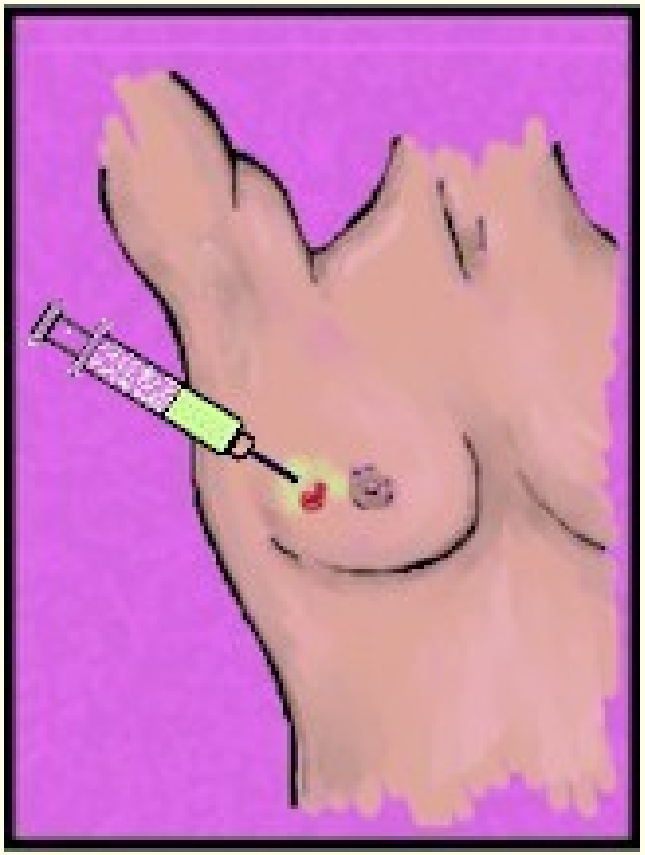
- Incidence in with Breast Cancer Treatment
  - 6-30%
  - Highly dependent on level of lymph node dissection or radiation therapy to the axilla
- Onset may be delayed several decades
- Characterized by a slowing of the circulation of lymph fluid
- Causes swelling in the arm and/or upper quadrant
- May cause discomfort in arm

Sentinel Lymph Node Dissection

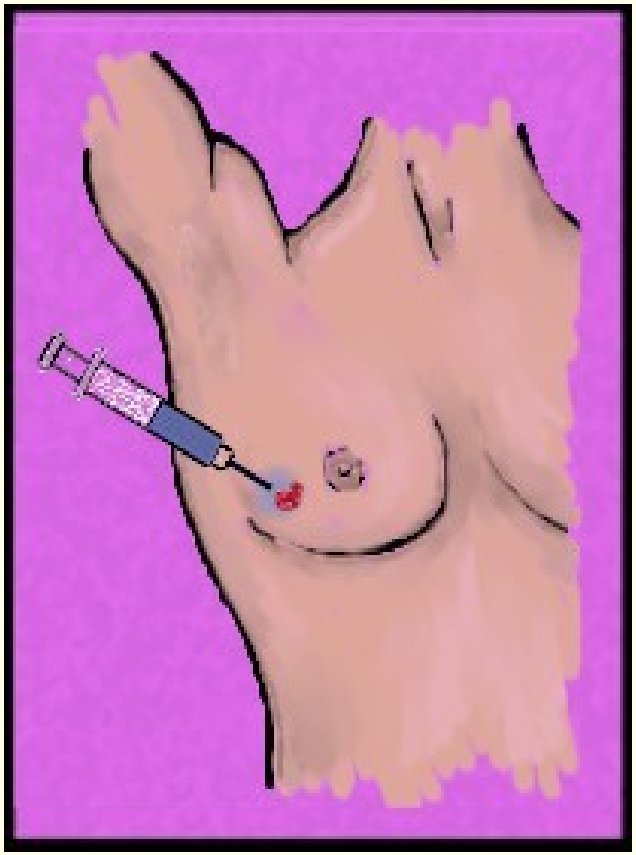
This technique may decrease unnecessary axillary lymph node dissections and the subsequent complications.

Sentinel Lymph Node Dissection

Sentinel Lymph Node Dissection (Injection Agent)

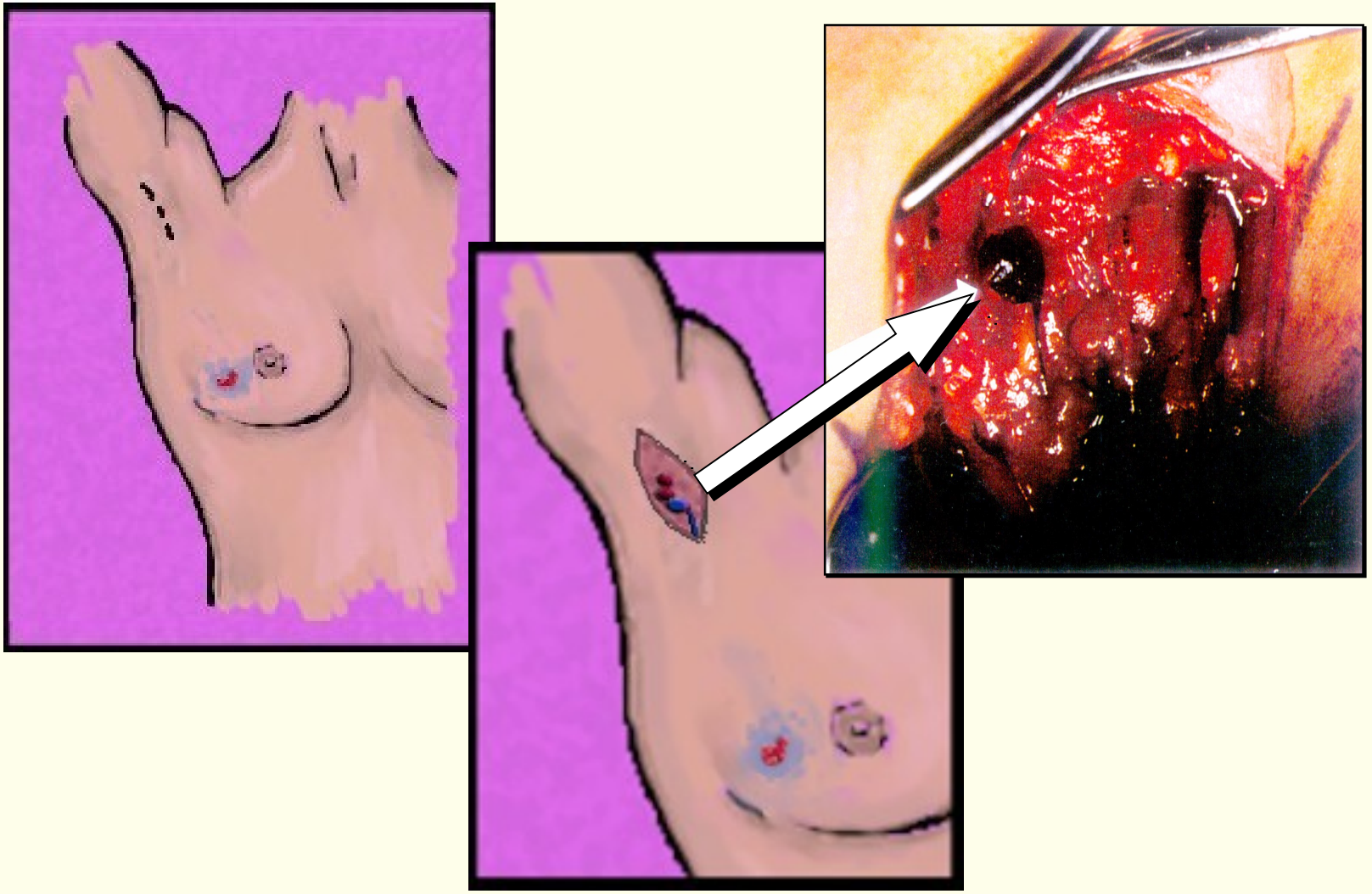


Technetium-99 sulfur colloid

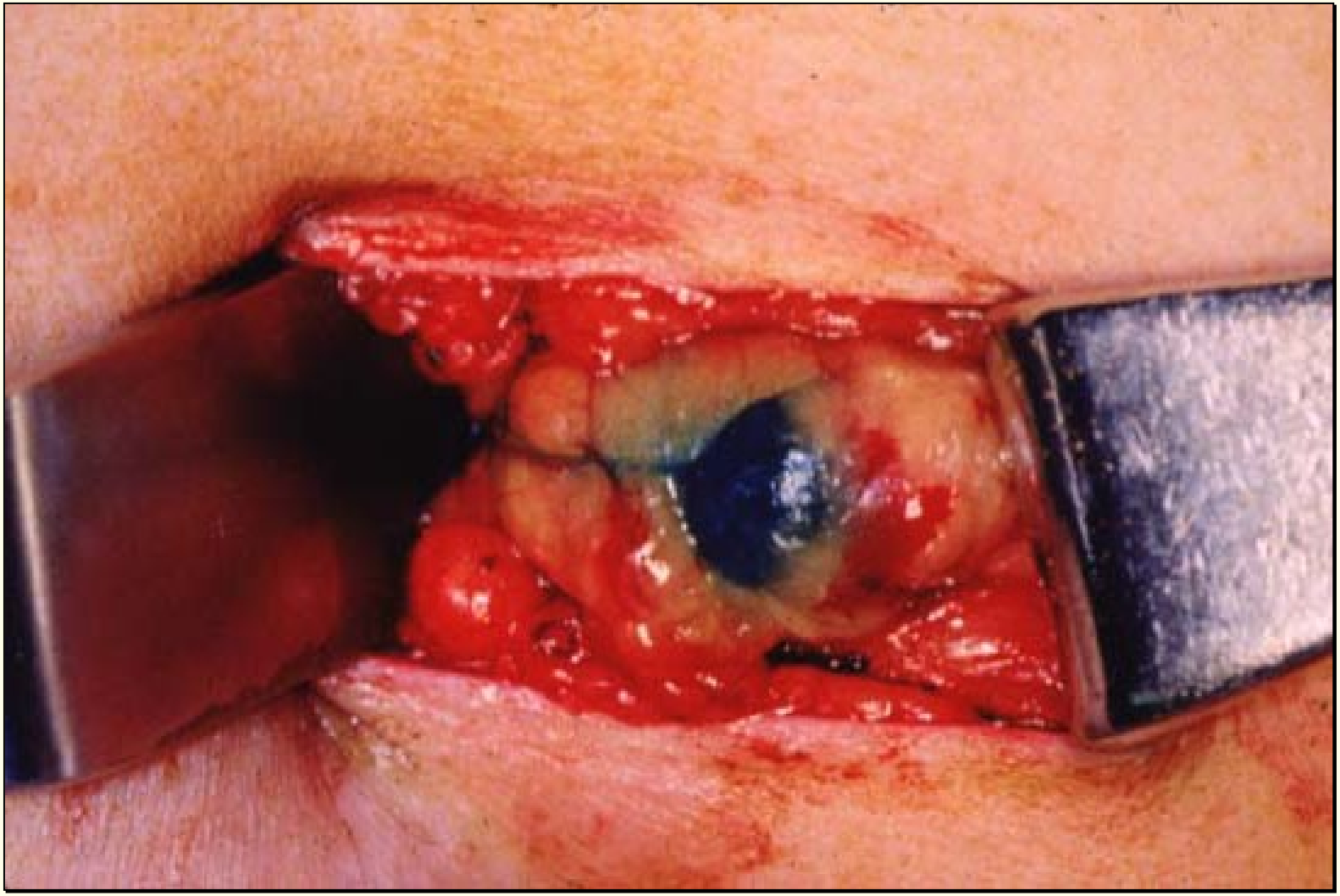


Isosulfan blue dye

Sentinel Lymph Node Dissection



Sentinel Lymph Node Dissection



Lumpectomy with SLND

NSABP Trial

Breast Cancer patients with clinically negative nodes:

- Group 1--sentinel node biopsy followed by axillary dissection.
- Group 2--sentinel node biopsy followed by axillary dissection only if the sentinel node is positive for cancer.

ACOS-OG Trial

Early breast cancer patients with positive sentinel nodes:

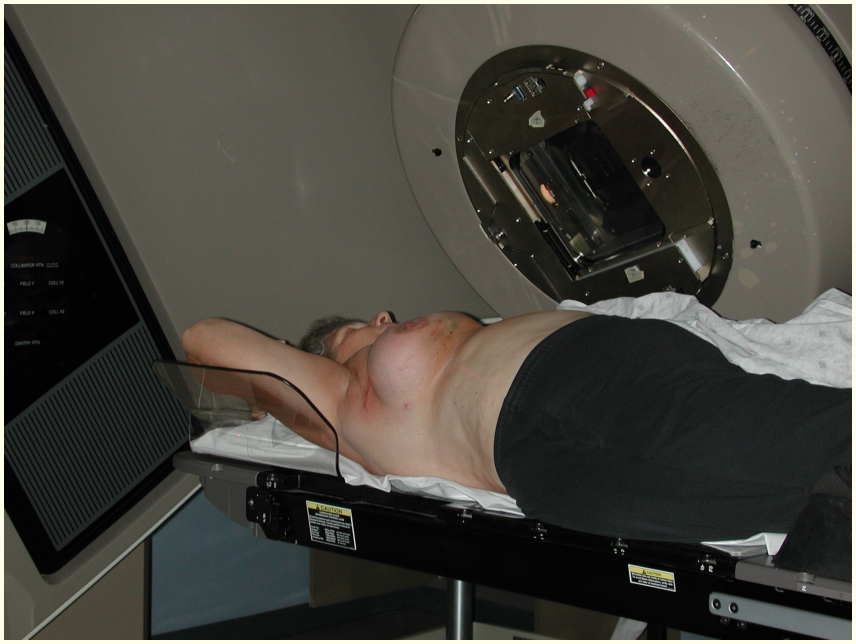
- Group 1—full axillary dissection
- Group 2—no further lymph node removed and no radiation to the axilla.

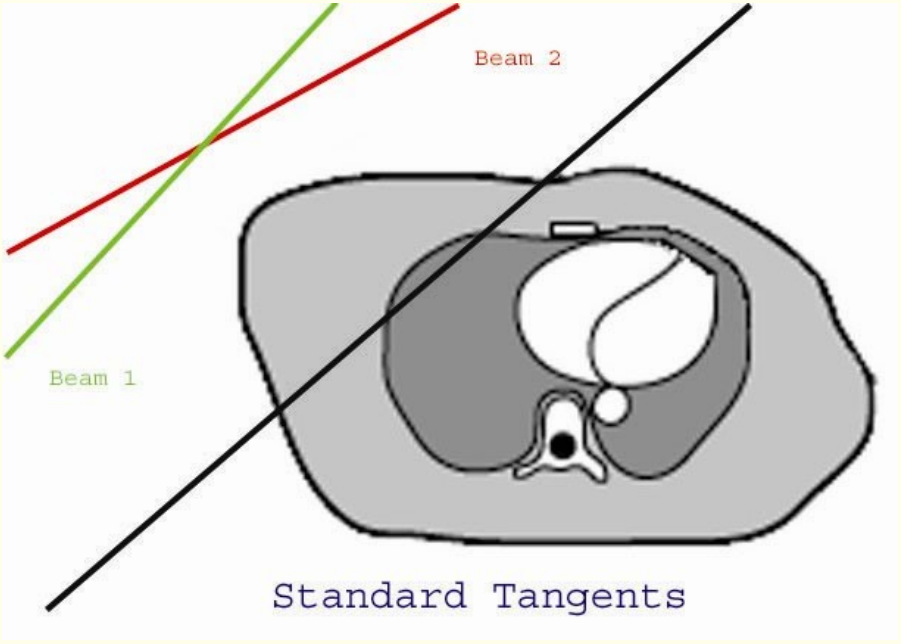
Women with negative sentinel nodes will have no further surgery.

Radiation Therapy

VARIAN

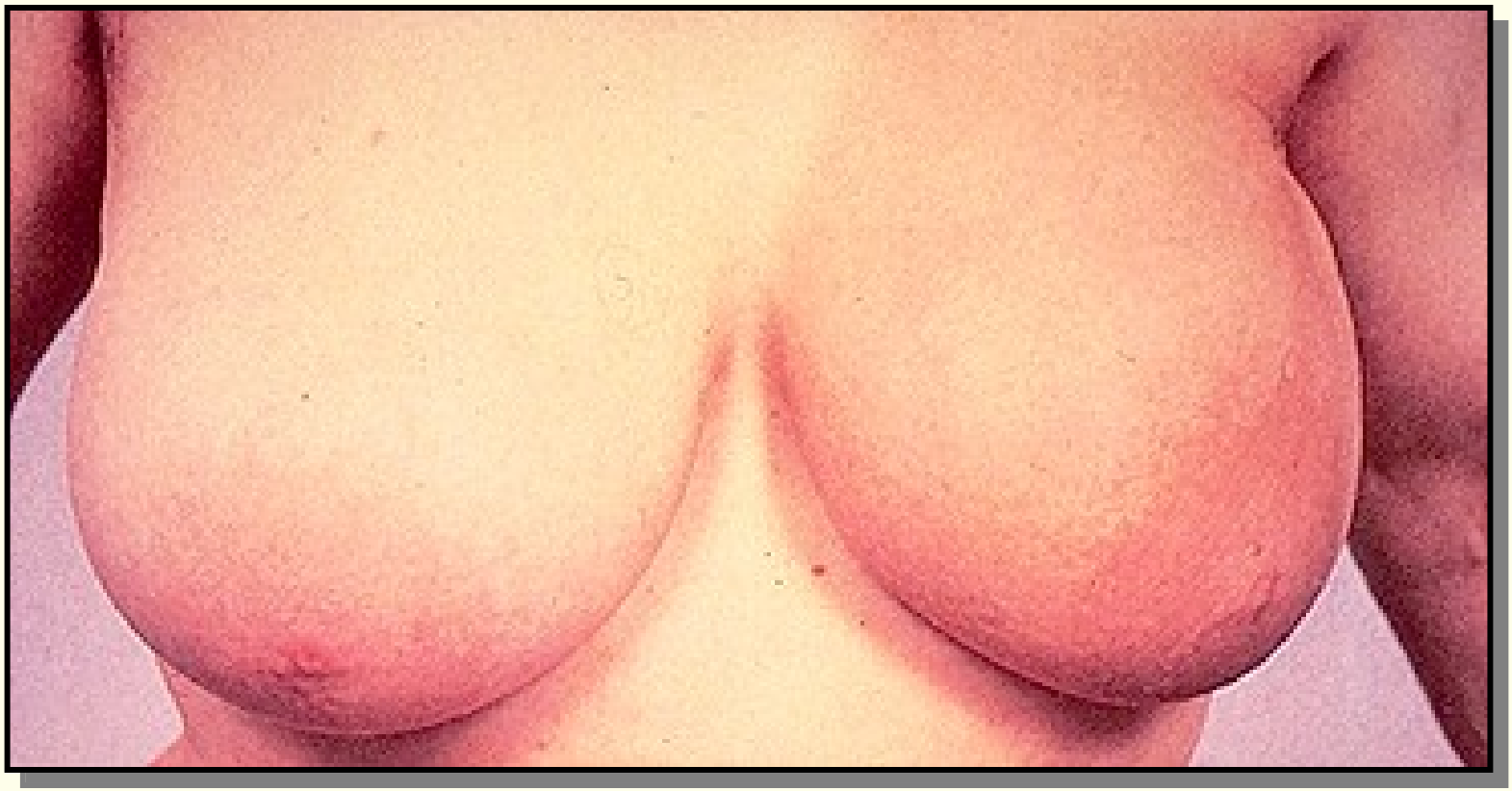
Tangential Fields



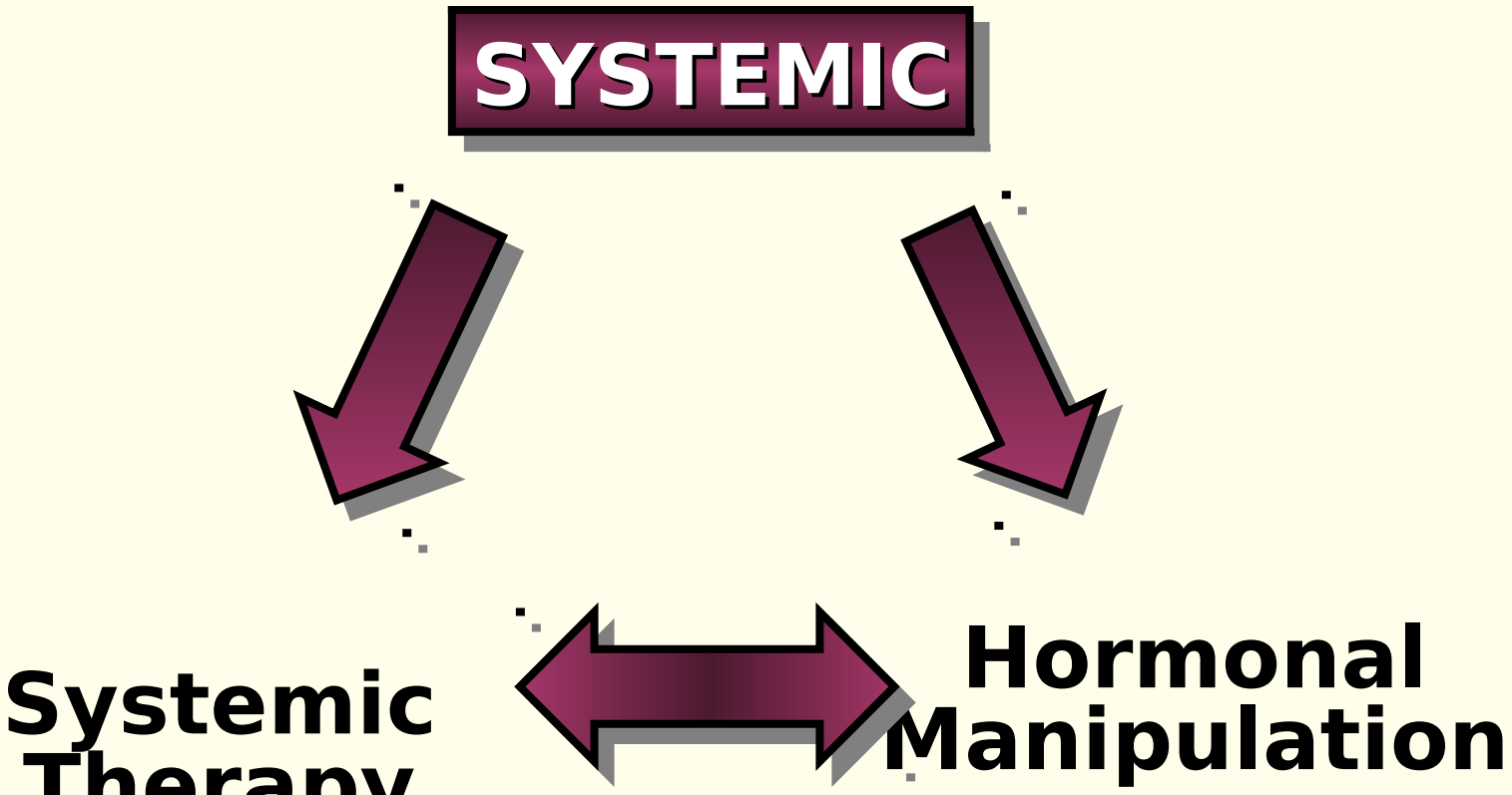


Acute Side Effects

- Fatigue
- Discomfort
- Skin Changes
  - Erythema
  - Hyperpigmentation
  - Dry or moist desquamation



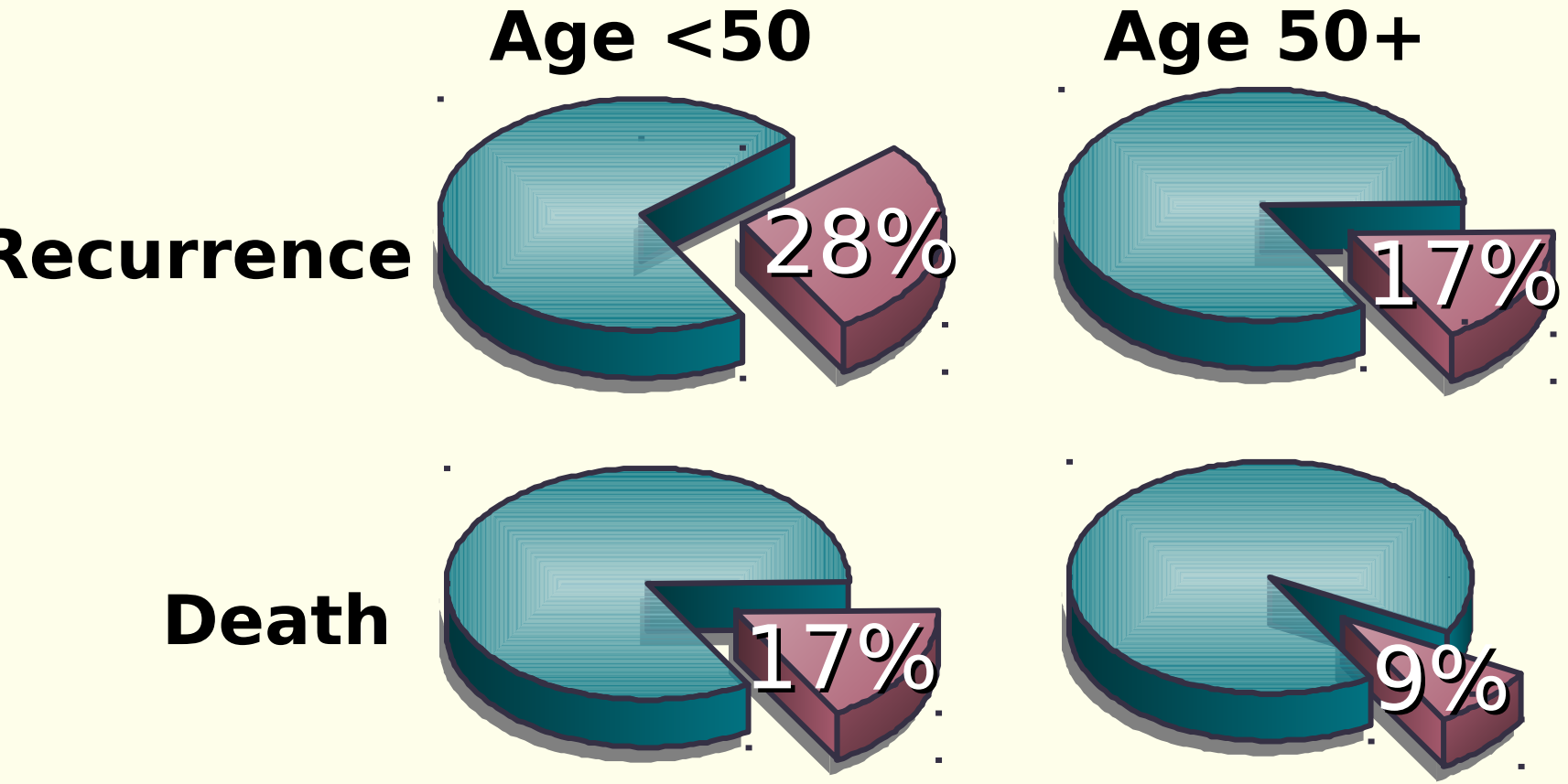
Systemic Therapy


SYSTEMIC
Systemic Therapy
Hormonal Manipulation

% Risk of Recurrence at 10 Years

	Tumor Size					
# pos nodes	< 1 cm	1-2 cm	2-3 cm	3-4 cm	4-5 cm	>5 cm
0	10	19	25	31	37	44
1-3	40	44	50	53	58	63
4-6	54	58	62	65	69	73
6-9	44	68	71	74	79	82
>10	78	81	83	84	86	87

Relative Reduction in Risk With Chemotherapy



Lancet 1992:339:1-15, 71-85

American Cancer Society

Adjuvant Systemic Agents in Breast Cancer Treatment

- **Chemotherapy**
  - **AC (Adriamycin + Cytoxan x 4)**
  - **FAC (5-FU + Adriamycin + Cytoxan)**
  - **AC/Taxol (AC + Taxol X 4)**
  - **TAC (Taxotere + Adriamycin + Cytoxan)**
  - **CMF (Cytoxan + Methotrexate + 5FU)**

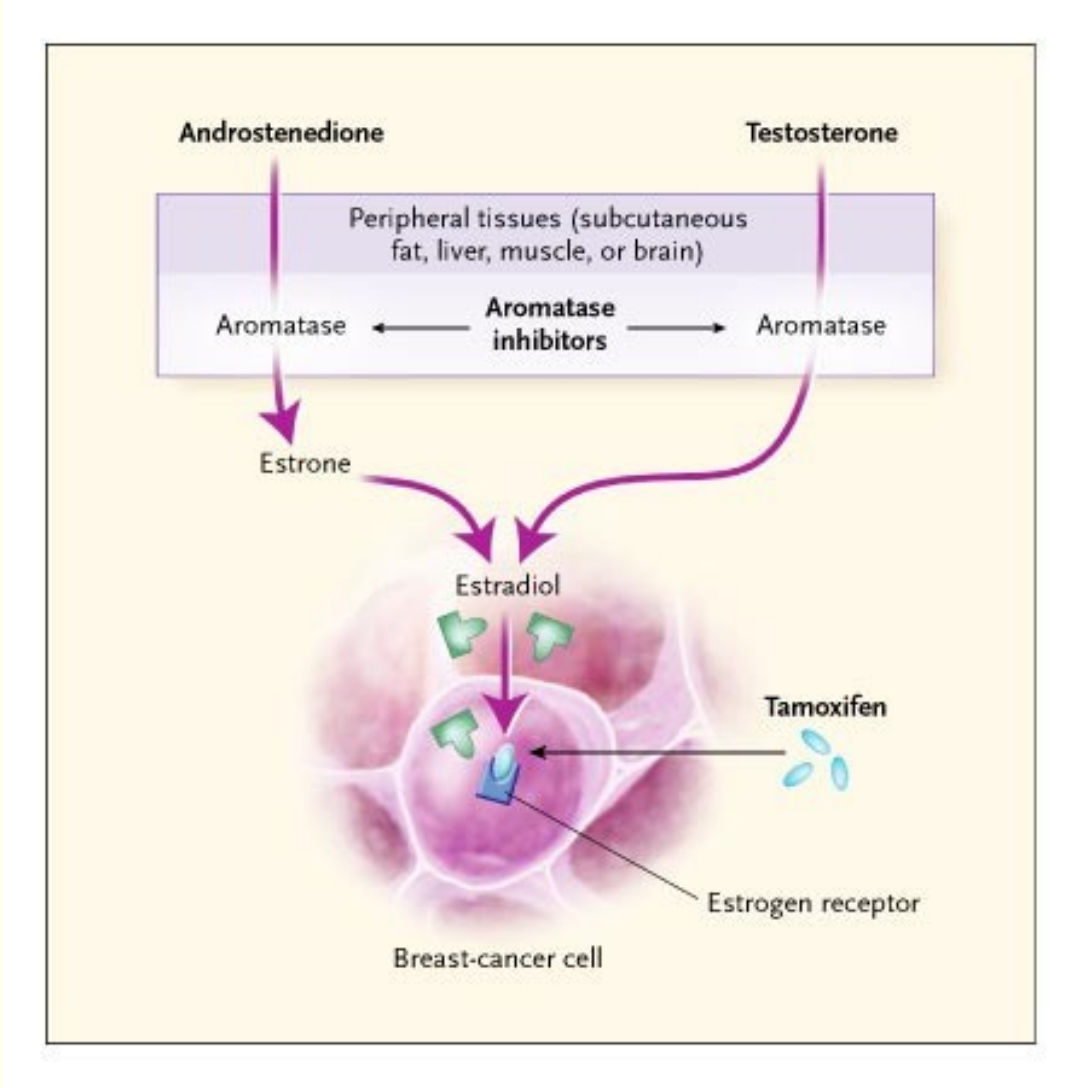
Side Effects of Chemotherapy

- Decreased blood counts
- Nausea/vomiting
- Hair loss
- Possibility of second cancer

Hormonal Therapy

- Tamoxifen
- Aromatase Inhibitor
  - Arimidex
  - Letrozole
  - Exemestane)
- Ovarian ablation

Mechanism of Action of Aromatase Inhibitors and Tamoxifen



Smith, I. E. et al. N Engl J Med 2003;348:2431-2442

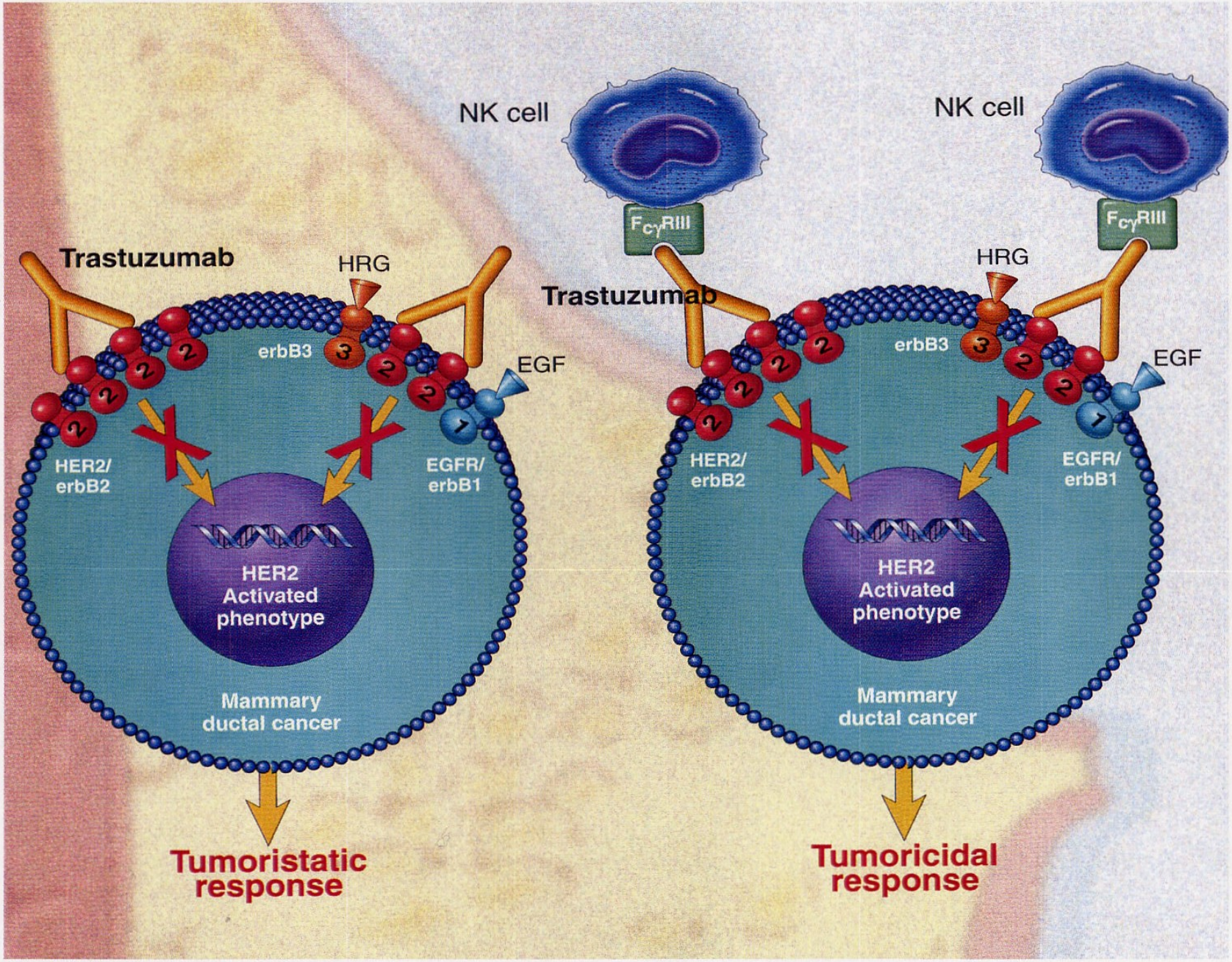
The NEW ENGLAND JOURNAL of MEDICINE

Proportional Reduction in Risk of Recurrence and Death with 5 Years of Adjuvant Tamoxifen

	Proportional Reduction			
	Recurrence		Death	
	%	P	%	p
ER+	50	0.00001	28	0.00001
ER+ PR+	37	0.00001	16	0.0001
ER+ PR -	46	0.00001	28	0.01
ER - PR+	23	0.05	9	NS
ER - PR -	<1	NS	<1	NS

Targeted Therapy

- Trastuzumab (Herceptin®)
- Mechanism of Action
  - Monoclonal antibodies targeted at the HER2/erbB2 receptors on overexpressed breast cancer cells
  - Inhibition of tumor cell proliferation (cytostatic)
  - Facilitation of immune function (cytotoxic)


NK cell
NK cell
FcγRIII
FcγRIII
Trastuzumab
Trastuzumab
HRG
HRG
erbB3
erbB3
EGF
EGF
HER2/
erbB2
HER2/
erbB2
EGFR/
erbB1
EGFR/
erbB1
HER2
Activated
phenotype
HER2
Activated
phenotype
Mammary
ductal cancer
Mammary
ductal cancer
Tumoristatic
response
Tumoricidal
response

Results of an Intention-to-Treat Analysis of the End Points

TABLE 2. RESULTS OF AN INTENTION-TO-TREAT ANALYSIS OF THE END POINTS.*

END POINT	CHEMOTHERAPY PLUS TRASTUZUMAB (N=235)	EITHER TYPE OF CHEMOTHERAPY ALONE (N=234)	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=138)	PACLITAXEL AND TRASTUZUMAB (N=92)	PACLITAXEL ALONE (N=96)
Median time to disease progression — mo	7.4	4.6	7.8	6.1	6.9	3.0
P value	<0.001		<0.001		<0.001	
Relative risk of progression (95% CI)	0.51 (0.41–0.63)		0.62 (0.47–0.81)		0.38 (0.27–0.53)	
Median time to treatment failure — mo	6.9	4.5	7.2	5.6	5.8	2.9
P value	<0.001		<0.001		<0.001	
Relative risk of treatment failure (95% CI)	0.58 (0.47–0.70)		0.67 (0.52–0.86)		0.46 (0.33–0.63)	
Median survival — mo	25.1	20.3	26.8	21.4	22.1	18.4
P value	0.046		0.16		0.17	
Relative risk of death (95% CI)	0.80 (0.64–1.00)		0.82 (0.61–1.09)		0.80 (0.56–1.11)	

*The time to treatment failure was defined as the time from randomization to disease progression, discontinuation of treatment for any reason, use of other types of antitumor therapy, or death. The final analysis of the primary end point (time to disease progression) was performed nine months after enrollment of the last patient. The most recent survival data were obtained 31 months after the enrollment of the last patient, with a median follow-up of 35 months (range, 30 to 51). As of the data-cutoff date of December 31, 1997, a total of 388 (83 percent) of the 469 patients had discontinued the study, including 173 (74 percent) of the 235 patients assigned to receive chemotherapy plus trastuzumab and 215 (92 percent) of the 234 patients assigned to receive chemotherapy alone. The response-evaluation committee assessed the tumor response in 446 patients: 99 percent of the 452 patients who had an assessment after the base-line evaluation and 95 percent of the 469 patients who enrolled in the study. In the group given paclitaxel and trastuzumab, the increase in the interval between randomization and disease progression was greater among patients who had a Karnofsky score of 90 or more at base line. The most common sites of disease progression among patients who received chemotherapy plus trastuzumab and among those who received chemotherapy alone were the liver (32 percent and 46 percent), the lungs (20 percent and 21 percent), bone (18 percent and 15 percent), and the central nervous system (18 percent and 9 percent). CI denotes confidence interval.

Slamon, D. J. et al. N Engl J Med 2001;344:783-792

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Herceptin® Clinical Trials
Side Effects Identified

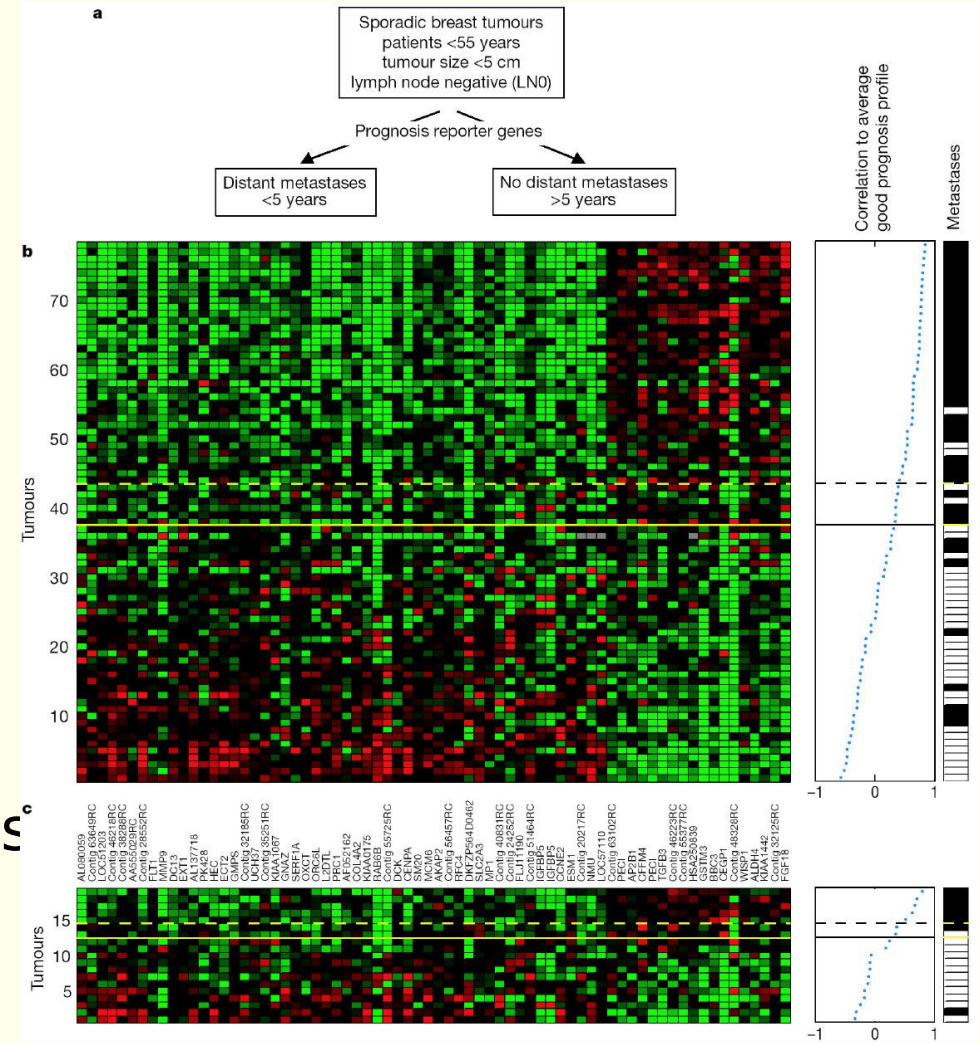
- Congestive heart failure
- Ventricular dysfunction
- Leukopenia
- Anemia
- Diarrhea
- Abdominal pain
- Infections
- Chills
- Fever
- Pain
- Weakness
- Nausea & vomiting
- Headache

Other Potential Treatment

- High dose chemotherapy with bone marrow or stem cell transplantation
- No better than standard chemotherapy

Future Direction?

- Microarray Technology
- Gene Expression Profiles
- Maybe used to tailor adjuvant treatments based on an individual's genes



Questions?